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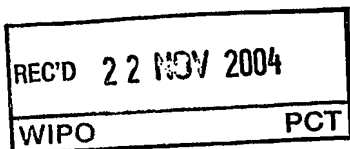


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INVESTOR IN PEOPLE



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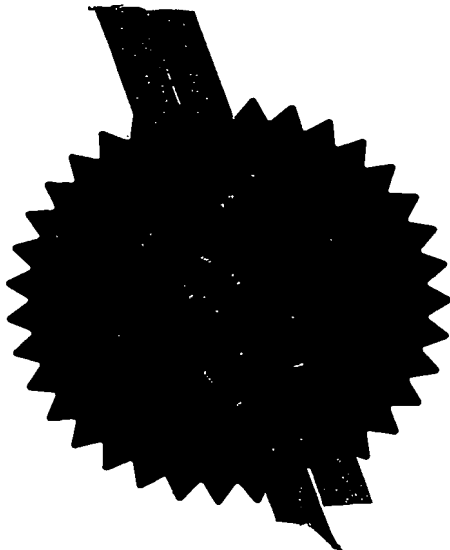
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P. Mahoney

Signed

Dated 9 November 2004

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1/77

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24 NOV 2003

The Patent Office

Cardiff Road
Newport
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1. Your reference

PC25572

25NOV03 E854665-2 D01298
P01/7700 0.00-0327323.2

2. Patent application number

(The Patent Office will fill in this part)

0327323.2

3. Full name, address and postcode of the or of each applicant (underline all surnames)

PFIZER LIMITED
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ

Patents ADP number (if you know it)

06892673001
United Kingdom

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

NOVEL PHARMACEUTICALS

5. Name of your agent (if you have one)

Dr. D. Kendrick

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

UK Patent Department
Pfizer Limited,
Ramsgate Road,
Sandwich, Kent,
CT13 9NJ
United Kingdom

Patents ADP number (if you know it)

00001271001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
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Patents Form 1/77

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| Description | 128 |
| Claim(s) | 21 |
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Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature

Date

24th November 2003

12. Name and daytime telephone number of person to contact in the United Kingdom
- | | |
|-----------------|--------------|
| Dr. D. Kendrick | 01304.646010 |
|-----------------|--------------|

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Novel Pharmaceuticals

The present invention relates to a series of novel 5,7-diaminopyrazolo[4,3-*d*] pyrimidines, which are cyclic guanylate monophosphate (cGMP)-specific phosphodiesterase type 5 inhibitors (hereinafter referred to as PDE-5 inhibitors) that are useful in the treatment of hypertension and other disorders, to processes for their preparation, intermediates used in their preparation, to compositions containing them and the uses of said compounds and compositions.

10

i) Hypertension

Blood pressure (BP) is defined by a number of haemodynamic parameters taken either in isolation or in combination. Systolic blood pressure (SBP) is the peak arterial pressure attained as the heart contracts. Diastolic blood pressure is the minimum arterial pressure attained as the heart relaxes. The difference between the SBP and the DBP is defined as the pulse pressure (PP).

15

Hypertension, or elevated BP, has been defined as a SBP of at least 140mmHg and/or a DBP of at least 90mmHg. By this definition, the prevalence of hypertension in developed countries is about 20% of the adult population, rising to about 60-70% of those aged 60 or more, although a significant fraction of these hypertensive subjects have normal BP when this is measured in a non-clinical setting. Some 60% of this older hypertensive population have isolated systolic hypertension (ISH), i.e. they have an elevated SBP and a normal DBP. Hypertension is associated with an increased risk of stroke, myocardial infarction, atrial fibrillation, heart failure, peripheral vascular disease and renal impairment (Fagard, RH; Am. J. Geriatric Cardiology 11(1), 23-28, 2002; Brown, MJ and Haycock, S; Drugs 59(Suppl 2), 1-12, 2000).

25

The pathophysiology of hypertension is the subject of continuing debate. While it is generally agreed that hypertension is the result of an imbalance between cardiac output and peripheral vascular resistance, and that most hypertensive subjects have abnormal cardiac output and increased peripheral resistance

30

there is uncertainty which parameter changes first (Beevers, G et al.; BMJ 322, 912-916, 2001).

Despite the large number of drugs available in various pharmacological categories, including diuretics, alpha-adrenergic antagonists, beta-adrenergic antagonists, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists, the need for an effective treatment of hypertension is still not satisfied.

10 ii) PDE5 inhibitors

Vascular endothelial cells secrete nitric oxide (NO). This acts on vascular smooth muscle cells and leads to the activation of guanylate cyclase and the accumulation of cyclic guanosine monophosphate (cGMP). The accumulation of cGMP causes the muscles to relax and the blood vessels to dilate. This dilation reduces vascular resistance and so leads to a reduction in blood pressure.

The cGMP is inactivated by hydrolysis to guanosine 5'-monophosphate (GMP) by a cGMP-specific phosphodiesterase. One important phosphodiesterase has been identified as Phosphodiesterase type 5 (PDE5). Inhibitors of PDE5 decrease the rate of hydrolysis of cGMP and so potentiate the actions of nitric oxide.

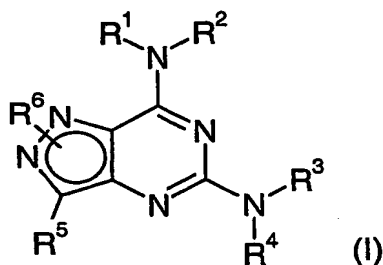
Inhibitors of PDE5 have been reported in several chemical classes, including: pyrazolo[4,3-d]pyrimidin-7-ones (e.g. published international patent applications WO 93/06104, WO 98/49166, WO 99/54333, WO 00/24745, WO 01/27112 and WO 01/27113); pyrazolo[3,4-d]pyrimidin-4-ones (e.g. published international patent application WO 93/07149); pyrazolo[4,3-d]pyrimidines (e.g. published international patent application WO 01/18004); quinazolin-4-ones (e.g. published international patent application WO 93/12095); pyrido[3,2-d]pyrimidin-4-ones (e.g. published international patent application WO 94/05661); purin-6-ones (e.g. published international patent application WO 94/00453); hexahydro-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-diones (e.g. published international

application WO 95/19978) and imidazo[5,1-f][1,2,4]triazin-ones (e.g. published international application WO 99/24433).

Although they have been suggested as agents for the treatment of related
5 conditions such as angina, PDE5 inhibitors have not yet been adopted as agents for the treatment of hypertension. PDE5 inhibitors are known for the treatment of male erectile dysfunction, e.g. sildenafil, tadalafil and vardenafil. There remains a demand for new PDE5 inhibitors, particularly with improved pharmacokinetic and pharmacodynamic properties. The compounds provided
10 herein are potent inhibitors of PDE5 that have improved selectivity *in vitro* and/or an extended half-life *in vivo*.

WO 02/00660 and WO 01/18004 disclose pyrazolo[4,3-d]pyrimidines with a
PDE-5 inhibiting effect, which can be used for treating disorders of the
15 cardiovascular system.

According to a first aspect, the present invention provides compounds of formula
(I)



20

wherein

R¹ is a cyclic group selected from R^A, R^B, R^C and R^D, each of which is optionally substituted with one or more R⁷ groups;

25 R² is hydrogen or C₁-C₂ alkyl;

R³ and R⁴ are each independently C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl or C₃-C₁₀ cycloalkyl, each of which is optionally substituted with one or more R⁸

groups, or R^E , which is optionally substituted with one or more R^9 groups, or hydrogen;

or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

5

R^5 is $-Y-CONR^{15}R^{16}$;

R^6 , which may be attached at N^1 or N^2 , is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted by C_1-C_6 alkoxy, C_1-C_6 haloalkoxy or a cyclic group selected from R^J , R^K , R^L and R^M , or R^6 is R^N , C_3-C_7 cycloalkyl or C_3-C_7 halocycloalkyl, each of which is optionally substituted by C_1-C_6 alkoxy or C_1-C_6 haloalkoxy, or R^6 is hydrogen;

R^7 is halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$ or CN ;

R^8 is halo, phenyl, C_1-C_6 alkoxyphenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$, CN , R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

R^9 is C_1-C_6 alkyl, C_1-C_6 haloalkyl or CO_2R^{12} ;

R^{10} is halo, C_3-C_{10} cycloalkyl, C_3-C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{13} , $CONR^{12}R^{13}$, CN , oxo, C_1-C_6 alkyl or C_1-C_6 haloalkyl, the last two of which are optionally substituted by R^{11} ;

R^{11} is phenyl, $NR^{12}R^{13}$ or $NR^{12}CO_2R^{14}$;

30

R^{12} and R^{13} are each independently hydrogen, C_1-C_6 alkyl or C_1-C_6 haloalkyl;

R^{14} is C_1-C_6 alkyl or C_1-C_6 haloalkyl;

R^{15} and R^{16} are each independently selected from

hydrogen,

C_1 - C_6 haloalkyl,

5 C_1 - C_6 alkyl optionally substituted with

R^{17} ,

$-NR^{18}R^{19}$,

$-CO_2R^{20}$,

$-CONR^{21}R^{22}$,

10 R^{23} or

phenyl optionally substituted by

halo,

C_1 - C_6 alkyl or

R^{17} ,

15 C_3 - C_7 cycloalkyl optionally substituted with

C_1 - C_6 alkyl,

R^{17} or

$-NR^{18}R^{19}$, and

R^{23} ;

20

or $NR^{15}R^{16}$ constitutes a 3- to 8-membered ring which may optionally include one or more further heteroatoms selected from nitrogen, oxygen and sulphur, and which may optionally be further substituted with R^{17} , C_1 - C_6 haloalkyl, $-CO_2R^{20}$, $-CONR^{21}R^{22}$, oxo or C_1 - C_6 alkyl optionally substituted by R^{17} ;

25

R^{17} is hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 (haloalkyl)oxy or C_3 - C_7 cycloalkyloxy;

R^{18} and R^{19} are each independently selected from hydrogen and C_1 - C_6 alkyl;

30

or $-NR^{18}R^{19}$ constitutes an azetidine, pyrrolidine, piperidine or morpholine ring;

R^{20} is hydrogen or C_1 - C_6 alkyl;

R^{21} and R^{22} are each independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl and C_3 - C_7 cycloalkyl;

5 or $-NR^{21}R^{22}$ constitutes a 3- to 8-membered ring which may optionally include one or more further heteroatoms selected from nitrogen, oxygen and sulphur;

R^{23} is a saturated 3- to 8-membered ring which includes at least one heteroatom selected from nitrogen, oxygen and sulphur, which ring may optionally be substituted by one or more C_1 - C_6 alkyl groups, provided that the group R^{23} is
10 joined to the parent molecule by a covalent bond to a carbon atom of said ring;

R^A and R^J are each independently a C_3 - C_{10} cycloalkyl or C_3 - C_{10} cycloalkenyl group, each of which may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic and which may be fused to either
15 (a) a monocyclic aromatic ring selected from a benzene ring and a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, or

(b) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;

20

R^B and R^K are each independently a phenyl or naphthyl group, each of which may be fused to

(a) a C_5 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl ring,
(b) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three
25 heteroatoms selected from nitrogen, oxygen and sulphur, or

(c) a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;

R^C , R^L and R^N are each independently a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated or partly unsaturated ring
30 system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, which ring may be fused to a C_5 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl group or a monocyclic aromatic

ring selected from a benzene ring and a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;

- 5 R^D and R^M are each independently a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur, which ring may further be fused to
- (a) a second 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;
 - (b) C_5 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl ring;
 - 10 (c) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur; or
 - (d) a benzene ring;

- 15 R^E , R^F and R^G are each independently a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

- 20 R^H is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur; and

Y is a covalent bond, C_1 - C_6 alkylenyl or C_3 - C_7 cycloalkylenyl;

- 25 a tautomer thereof or a pharmaceutically acceptable salt, solvate or polymorph of said compound or tautomer.

- 30 As used herein, alkylenyl indicates an alkyl- m,n -diyl unit where m and n are the same or different, such as methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$) and propane-1,2-diyl ($-\text{CH}(\text{CH}_3)\text{CH}_2-$).

As used herein, cycloalkylenyl indicates a cycloalkyl- m,n -diyl unit where m and n are the same or different, such as cyclopropane-1,1-diyl and cyclohexane-1,4-diyl.

Unless otherwise indicated, an alkyl or alkoxy group may be straight or branched and contain 1 to 8 carbon atoms, preferably 1 to 6 and particularly 1 to 4 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, pentyl and hexyl. Examples of alkoxy include methoxy, ethoxy, isopropoxy and n-butoxy.

Unless otherwise indicated, an alkenyl or alkynyl group may be straight or branched and contain 2 to 8 carbon atoms, preferably 2 to 6 and particularly 2 to 4 carbon atoms and may contain up to 3 double or triple bonds which may be conjugated. Examples of alkenyl and alkynyl include vinyl, allyl, butadienyl and propargyl.

Unless otherwise indicated, a cycloalkyl or cycloalkoxy group may contain 3 to 10 ring-atoms, may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic. Examples of cycloalkyl groups are cyclopropyl, cyclopentyl, cyclohexyl and adamantyl.

Unless otherwise indicated, a cycloalkenyl group may contain 3 to 10 ring-atoms, may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic and may contain up to 3 double bonds. Examples of cycloalkenyl groups are cyclopentenyl and cyclohexenyl.

Aryl includes phenyl, naphthyl, anthracenyl and phenanthrenyl.

Unless otherwise indicated, a heteroalicycyl group contains 3 to 10 ring-atoms up to 4 of which may be hetero-atoms such as nitrogen, oxygen and sulfur, and may be saturated or partially unsaturated. Examples of heteroalicycyl groups are oxiranyl, azetidiny, tetrahydrofuranyl, thiolanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, sulfolanyl, dioxolanyl, dihydropyranyl, tetrahydropyranyl, piperidinyl, pyrazolinyl, pyrazolidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, azepinyl, oxazepinyl, thiazepinyl, thiazolinyl and diazapanyl.

Unless otherwise indicated, a heteroaryl group contains 3 to 10 ring-atoms up to 4 of which may be hetero-atoms such as nitrogen, oxygen and sulfur. Examples of heteroaryl groups are furyl, thienyl, pyrrolyl; oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, triazinyl. In addition, the term heteroaryl includes fused heteroaryl groups, for example benzimidazolyl, benzoxazolyl, imidazopyridinyl, benzoxazinyl, benzothiazinyl, oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, benzothiazolyl, phthalimido, benzofuranyl, benzodiazepinyl, indolyl and isoindolyl.

Halo means fluoro, chloro, bromo or iodo.

Haloalkyl includes monohaloalkyl, polyhaloalkyl and perhaloalkyl, such as 2-bromoethyl, 2,2,2-trifluoroethyl, chlorodifluoromethyl and trichloromethyl. Haloalkoxy includes monohaloalkoxy, polyhaloalkoxy and perhaloalkoxy, such as 2-bromoethoxy, 2,2,2-trifluoroethoxy, chlorodifluoromethoxy and trichloromethoxy. Halocycloalkyl includes monohalocycloalkyl, polyhalocycloalkyl and perhalocycloalkyl.

Unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

In one preferred embodiment, R^1 is R^A , which is optionally substituted with one or more R^7 groups; and

R^A is a C_3 - C_{10} cycloalkyl group, which may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic, which may be fused to either

(a) a monocyclic aromatic ring selected from a benzene ring and a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, or

(b) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur.

Preferably, R^A is a monocyclic C_3 - C_8 cycloalkyl group.

5

More preferably, R^A is a monocyclic C_5 - C_7 cycloalkyl group.

Most preferably, R^A is cyclopentyl or cyclohexyl.

10 In another preferred embodiment, R^1 is R^B , which is optionally substituted with one or more R^7 groups.

Preferably, R^B is phenyl.

15 In another preferred embodiment, R^1 is R^C , which is optionally substituted with one or more R^7 groups.

Preferably, R^C is a monocyclic saturated or partly unsaturated ring system containing between 3 and 8 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

20

More preferably, R^C is a monocyclic saturated or partly unsaturated ring system containing between 5 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

25

Most preferably, R^C is a monocyclic saturated ring system containing between 5 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

30 In another preferred embodiment, R^1 is R^D , which is optionally substituted with one or more R^7 groups.

Preferably, R^D is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur.

5 More preferably, R^D is a 5-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur and optionally up to two further nitrogen atoms in the ring, or a 6-membered heteroaromatic ring including 1, 2 or 3 nitrogen atoms.

10 More preferably R^D is furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl.

Most preferably, R^D is pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl.

15 Preferably, R^7 is halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, OR^{12} or $CONR^{12}R^{13}$.

More preferably, R^7 is halo, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, hydroxy or $CONH(C_1$ - C_3 alkyl).

20 Most preferably, R^7 is fluoro, methyl, ethyl, hydroxy, methoxy, propoxy or $CONHMe$.

Preferably, R^2 is hydrogen or methyl.

25 More preferably, R^2 is hydrogen.

30 Preferably, R^3 is hydrogen, C_1 - C_6 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups; and wherein R^E is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

More preferably, R^3 is hydrogen, C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups; and wherein R^E is a monocyclic saturated ring system containing
5 between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

In one preferred embodiment, R^3 is R^E , which is optionally substituted with one or more R^9 groups and wherein R^E is a monocyclic saturated ring system
10 containing between 3 and 7 ring atoms containing one nitrogen atom.

More preferably, R^E is azetidiny, pyrrolidinyl or piperidinyl.

In another preferred embodiment, R^3 is C_1 - C_4 alkyl, which is optionally
15 substituted with one or more R^8 groups and wherein R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $NR^{12}R^{13}$, $NR^{12}CO_2R^{14}$, CO_2R^{12} , $CONR^{12}R^{13}$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups.

More preferably, R^8 is hydroxy, methoxy, methoxyphenyl, NH_2 , $NHMe$, NMe_2 ,
20 $NHCO_2^tBu$, $NMeCO_2^tBu$, CO_2H , $CONHMe$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups.

In one preferred embodiment, R^8 is R^G , which is optionally substituted with one or more R^9 groups and wherein R^G is a monocyclic saturated ring system
25 containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.

More preferably, R^G is a monocyclic saturated ring system containing between 3 and 7 ring atoms containing one nitrogen atom and optionally one oxygen atom.
30

Most preferably, R^G is pyrrolidinyl, piperidinyl or morpholinyl.

In another preferred embodiment, R^8 is R^H , which is optionally substituted with one or more R^9 groups and wherein R^H is a 5- or 6-membered heteroaromatic ring containing up to two nitrogen atoms.

5 More preferably, R^H is pyrazolyl.

Preferably, R^9 is methyl or CO_2^tBu .

10 In another preferred embodiment, R^3 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl, which is optionally substituted with one or more R^8 groups, or R^3 is azetidiny, pyrrolidinyl or piperidinyl, each of which is optionally substituted with one or more R^9 groups, wherein

R^8 is hydroxy, methoxy, methoxyphenyl, NH_2 , NHMe , NMe_2 , NHCO_2^tBu , $\text{NMeCO}_2^t\text{Bu}$, CO_2H , CONHMe , pyrrolidinyl, piperidinyl, morpholinyl or pyrazolyl, the last four of which are optionally substituted with one or more R^9 groups and wherein

15 R^9 is methyl or CO_2^tBu .

20 In one preferred embodiment, R^4 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl or $\text{C}_2\text{-C}_6$ alkynyl.

More preferably, R^4 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_6$ haloalkyl.

25 Most preferably, R^4 is hydrogen, methyl or ethyl.

30 In another preferred embodiment, $-\text{NR}^3\text{R}^4$ forms R^F , which is optionally substituted with one or more R^{10} groups and wherein R^F is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms containing at least one nitrogen atom and optionally one other atom selected from oxygen and sulphur.

More preferably, R^F is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring

atoms containing one or two nitrogen atoms and optionally one other atom selected from oxygen and sulphur.

Most preferably, R^F is selected from azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, 3-azabicyclo[3.1.0]hex-3-yl, homopiperaziny, 2,5-diazabicyclo[4.3.0]non-2-yl, 3,8-diazabicyclo[3.2.1]oct-3-yl, 3,8-diazabicyclo[3.2.1]oct-8-yl, 1,4-diazabicyclo[4.3.0]non-4-yl and 1,4-diazabicyclo[3.2.2]non-4-yl.

10 Preferably R^{10} is halo, OR^{12} , $NR^{12}R^{13}$, $NR^{12}CO_2R^{14}$, CO_2R^{13} , oxo, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, the last two of which are optionally substituted by R^{11} .

More preferably, R^{10} is halo, methyl, ethyl, isopropyl, hydroxy, methoxy, NH_2 , $NHMe$, NMe_2 , $NHCO_2^tBu$, CO_2H , CO_2^tBu , oxo, benzyl, $-CH_2NH_2$, $-CH_2NHMe$, 15 CH_2NMe_2 or $-CH_2NMeCO_2^tBu$.

Preferably R^5 is $-CONR^{15}R^{16}$, i.e. a group $-Y-CONR^{15}R^{16}$ wherein Y is a covalent bond. Preferably R^{15} and R^{16} are each independently selected from hydrogen, C_1 - C_6 alkyl optionally substituted with R^{17} , $-NR^{18}R^{19}$, $-CO_2R^{20}$, 20 $-CONR^{21}R^{22}$, R^{23} or phenyl optionally substituted by halo, C_1 - C_6 alkyl or R^{17} , C_3 - C_7 cycloalkyl and R^{23} , or $NR^{15}R^{16}$ constitutes a 5- to 7-membered ring which may optionally include one or more further heteroatoms selected from nitrogen and oxygen, and which may optionally be further substituted with R^{17} , $-CO_2R^{20}$, $-CONR^{21}R^{22}$ or C_1 - C_6 alkyl optionally substituted by R^{17} . More preferably R^{15} 25 and R^{16} are each independently selected from hydrogen and C_1 - C_6 alkyl optionally substituted with R^{17} or $-NR^{18}R^{19}$.

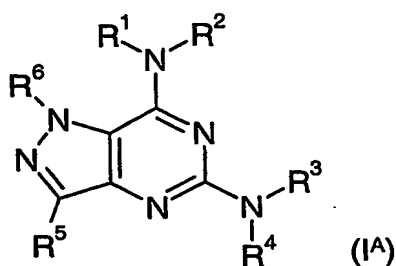
Preferably, R^{17} is hydroxy, C_1 - C_6 alkoxy or C_3 - C_7 cycloalkyloxy;

30 Preferably, R^{21} and R^{22} are each independently selected from hydrogen, C_1 - C_6 alkyl, and C_3 - C_7 cycloalkyl, or $-NR^{21}R^{22}$ constitutes a 5- to 8-membered ring which may optionally include one or more further heteroatoms selected from nitrogen and oxygen.

Preferably, R^{23} is a saturated 5- to 7-membered ring which includes at least one heteroatom selected from nitrogen and oxygen, which ring may optionally be substituted by one or more C_1 - C_6 alkyl groups.

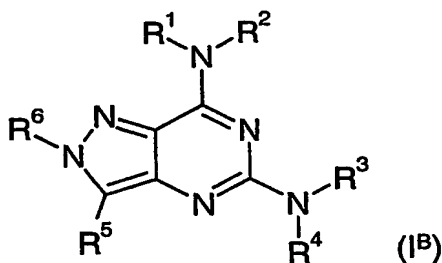
5

Preferably, R^6 is positioned on N^1 to give the compound of formula (I^A):



10

In an alternative embodiment of the present invention, R^6 may be positioned on N^2 to give the compound of formula (I^B):



15

Preferably, R^6 is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, each of which is optionally substituted by C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy or a cyclic group selected from R^J , R^L and R^M , or R^6 is R^N or hydrogen;

R^J is a C_3 - C_7 monocyclic cycloalkyl group;

20 R^L and R^N are each independently a monocyclic, saturated or partly unsaturated ring system containing between 4 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur; and

R^M is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur.

More preferably, R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy or a cyclic group selected from R^J , R^L and R^M , or R^6 is R^N or hydrogen;

5 R^J is cyclopropyl or cyclobutyl;

R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur; and

10 R^M is a 5- or 6-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur.

More preferably, R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy or a cyclic group selected from R^J , R^L and R^M , or R^6 is R^N or hydrogen;

15 R^J is cyclopropyl or cyclobutyl;

R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms containing one heteroatom selected from nitrogen, oxygen and sulphur; and

R^M is a 5- or 6-membered heteroaromatic ring containing one nitrogen atom.

20

More preferably, R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy, cyclopropyl, cyclobutyl, tetrahydrofuranyl, tetrahydropyranyl or pyridinyl, or R^6 is hydrogen or tetrahydropyranyl.

25 Most preferably, R^6 is hydrogen, methyl, ethyl, isopropyl, isobutyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, propoxyethyl, 2,2,2-trifluoroethyl, tetrahydrofuranylmethyl, tetrahydropyranylmethyl, tetrahydropyranyl or pyridinylmethyl.

30 Preferred embodiments of compounds of formula (I) are those that incorporate two or more of the foregoing preferences.

Preferably R^1 is a cyclic group selected from R^A , R^B , R^C and R^D , each of which is optionally substituted with one or more R^7 groups;

R^2 is hydrogen or C_1 - C_2 alkyl;

5

R^3 is hydrogen, C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups;

R^4 is hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

10

or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy or a cyclic group selected from R^J , R^L and R^M , or

15

R^6 is R^N or hydrogen;

R^7 is halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$ or CN ;

20

R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$, CN , R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

25

R^9 is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or CO_2R^{12} ;

R^{10} is halo, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{13} , $CONR^{12}R^{13}$, CN , oxo, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, the last two of which are optionally substituted by R^{11} ;

30

R^{11} is phenyl, $NR^{12}R^{13}$ or $NR^{12}CO_2R^{14}$;

R^{12} and R^{13} are each independently hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^{14} is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

5 R^A is a monocyclic C_3 - C_8 cycloalkyl group;

R^B is phenyl;

10 R^C is a monocyclic saturated or partly unsaturated ring system containing between 3 and 8 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

15 R^D is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur;

R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

20 R^F and R^G are each independently a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

25 R^H is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur;

R^J is cyclopropyl or cyclobutyl;

30 R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^M is a 5- or 6-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur; and

Y is a covalent bond.

5

More preferably, R^1 is a cyclic group selected from R^A , R^B , R^C and R^D , each of which is optionally substituted with one or more R^7 groups;

R^2 is hydrogen or C_1 - C_2 alkyl;

10

R^3 is hydrogen, C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups;

R^4 is hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

15

or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy or a cyclic group selected from R^J , R^L and R^M , or

20

R^6 is R^N or hydrogen;

R^7 is halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, OR^{12} or $CONR^{12}R^{13}$;

25 R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $NR^{12}R^{13}$, $NR^{12}CO_2R^{14}$, CO_2R^{12} , $CONR^{12}R^{13}$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

R^9 is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or CO_2R^{12} ;

30 R^{10} is halo, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{13} , $CONR^{12}R^{13}$, CN, oxo, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, the last two of which are optionally substituted by R^{11} ;

R¹¹ is phenyl, NR¹²R¹³ or NR¹²CO₂R¹⁴;

R¹² and R¹³ are each independently hydrogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

5

R¹⁴ is C₁-C₆ alkyl or C₁-C₆ haloalkyl;

R¹⁵ and R¹⁶ are each independently selected from hydrogen, C₁-C₆ alkyl optionally substituted with R¹⁷, -NR¹⁸R¹⁹, -CO₂R²⁰, -CONR²¹R²², R²³ or phenyl optionally substituted by halo, C₁-C₆ alkyl or R¹⁷, C₃-C₇ cycloalkyl and R²³, or NR¹⁵R¹⁶ constitutes a 5- to 7-membered ring which may optionally include one or more further heteroatoms selected from nitrogen and oxygen, and which may optionally be further substituted with R¹⁷, -CO₂R²⁰, -CONR²¹R²² or C₁-C₆ alkyl optionally substituted by R¹⁷;

15

R¹⁷ is hydroxy, C₁-C₆ alkoxy or C₃-C₇ cycloalkyloxy;

R²¹ and R²² are each independently selected from hydrogen, C₁-C₆ alkyl, and C₃-C₇ cycloalkyl, or -NR²¹R²² constitutes a 5- to 8-membered ring which may optionally include one or more further heteroatoms selected from nitrogen and oxygen;

20

R²³ is a saturated 5- to 7-membered ring which includes at least one heteroatom selected from nitrogen and oxygen, which ring may optionally be substituted by one or more C₁-C₆ alkyl groups;

25

R^A is a monocyclic C₅-C₇ cycloalkyl group;

R^B is phenyl;

30

R^C is a monocyclic saturated ring system containing between 5 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^D is a 5-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur and optionally up to two further nitrogen atoms in the ring, or a 6-membered heteroaromatic ring including 1, 2 or 3 nitrogen atoms;

5

R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms containing one nitrogen atom;

10 R^F is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms containing at least one nitrogen atom and optionally one other atom selected from oxygen and sulphur;

15 R^G is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

20 R^H is a 5- or 6-membered heteroaromatic ring containing up to two nitrogen atoms;

25 R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^M is a 5- or 6-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur; and

Y is a covalent bond.

30

Most preferred compounds are:

1-(2-ethoxyethyl)-*N*-ethyl-5-(ethylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

5 5-(dimethylamino)-1-(2-ethoxyethyl)-*N*-methyl-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

5-(dimethylamino)-1-(2-ethoxyethyl)-*N*-(2-(methylamino)ethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

10 5-(dimethylamino)-*N*-(2-(dimethylamino)ethyl)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

5-(dimethylamino)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-*N*-(piperidin-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

15

5-(dimethylamino)-1-(2-ethoxyethyl)-*N*-(2-methoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

20 (2*R*)-2-[[5-(dimethylamino)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]amino]propionic acid,

3-[[5-(dimethylamino)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]amino]propionic acid,

25 1-(2-ethoxyethyl)-*N*-methyl-7-(4-methylpyridin-2-ylamino)-5-(piperazin-1-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

1-(2-ethoxyethyl)-*N*-methyl-5-((3*R*)-3-methylpiperazin-1-yl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

30

1-(2-ethoxyethyl)-*N*-ethyl-5-((3*R*)-3-methylpiperazin-1-yl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

- 1-(2-ethoxyethyl)-5-(ethylamino)-*N*-methyl-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,
- 5 1-(2-ethoxyethyl)-*N*-(2-methoxyethyl)-5-(methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,
- 5-(dimethylamino)-1-(2-ethoxyethyl)-*N*-(2-hydroxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,
- 10 1-(2-ethoxyethyl)-5-(ethylamino)-*N*-(2-methoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,
- 1-(2-ethoxyethyl)-5-(*N*-(2-hydroxyethyl)-*N*-methylamino)-*N*-methyl-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,
- 15 1-(2-ethoxyethyl)-5-((2-methoxyethyl)amino)-*N*-methyl-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,
- 7-(cyclohexylamino)-1-(2-ethoxyethyl)-*N*-methyl-5-((3*R*)-3-methylpiperazin-1-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide, and
- 20 1-(2-ethoxyethyl)-*N*-methyl-5-[*N*-methyl-*N*-((3*S*)-1-methylpyrrolidin-3-yl)amino]-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide
- 25 and tautomers thereof and pharmaceutically acceptable salts, solvates and polymorphs of said compounds or tautomers.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts thereof.

30

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate,

esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of a compound of formula (I) may be readily prepared by mixing together solutions of the compound of formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more

organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Halebian (August 1975).

5

Hereinafter all references to compounds of formula (I) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

- 10 The compounds of the invention include compounds of formula (I) as hereinbefore defined, polymorphs, prodrugs, and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (I).
- 15 As stated, the invention includes all polymorphs of the compounds of formula (I) as hereinbefore defined.

- Also within the scope of the invention are so-called 'prodrugs' of the compounds of formula (I). Thus certain derivatives of compounds of formula (I) which may
- 20 have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-
- 25 drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

- Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with
- 30 certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include:

(i) where the compound of formula (I) contains a carboxylic acid functionality (-COOH), an ester thereof, for example, replacement of the hydrogen with (C₁-C₈)alkyl;

5

(ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C₁-C₆)alkanoyloxymethyl; and

10 (iii) where the compound of formula (I) contains a primary or secondary amino functionality (-NH₂ or -NHR where R ≠ H), an amide thereof, for example, replacement of one or both hydrogens with (C₁-C₁₀)alkanoyl.

Further examples of replacement groups in accordance with the foregoing
15 examples and examples of other prodrug types may be found in the aforementioned references.

Finally, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

20

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis/trans* (or *Z/E*) isomers are possible. Where the compound contains, for example, a keto or oxime group or
25 an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I),
30 including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

5

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

10

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

15

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

25

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).

30

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I ,
5 nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulphur, such as ^{35}S .

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue
10 distribution studies. The radioactive isotopes tritium, *i.e.* ^3H , and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^2H , may afford certain
15 therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be
20 useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes
25 analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include
30 those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O , d_6 -acetone, d_6 -DMSO.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or
5 radio frequency drying may be used for this purpose.

The compounds of formula (I) are inhibitors of PDE5. Accordingly, in a further aspect the present invention provides for the use of a compound of formula (I), or a tautomer, salt or solvate thereof, as a pharmaceutical agent, and particularly
10 as a therapeutic agent for the treatment of a condition where inhibition of PDE5 is known, or can be shown, to produce a beneficial effect.

The term "treatment" includes palliative, curative and prophylactic treatment.

15 Conditions suitable for treatment with the compounds of the invention include hypertension (including essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension), congestive heart failure, angina (including stable, unstable and
20 variant (Prinzmetal) angina), stroke, coronary artery disease, congestive heart failure, conditions of reduced blood vessel patency (such as post-percutaneous coronary angioplasty), peripheral vascular disease, atherosclerosis, nitrate-induced tolerance, nitrate tolerance, diabetes, impaired glucose tolerance, metabolic syndrome, obesity, sexual dysfunction (including male erectile
25 disorder, impotence, female sexual arousal disorder, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual pain disorder, female sexual orgasmic dysfunction and sexual dysfunction due to spinal cord injury), premature labour, pre-eclampsia, dysmenorrhea, polycystic ovary syndrome, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, chronic
30 obstructive pulmonary disease, acute respiratory failure, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, gut motility disorders (including irritable bowel syndrome), Kawasaki's syndrome, multiple sclerosis, Alzheimer's disease, psoriasis, skin necrosis, scarring, fibrosis, pain (particularly neuropathic pain),

cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and haemorrhoids.

5 In a further aspect, the present invention provides for the use of a compound of formula (I), or a tautomer, salt or solvate thereof, for the manufacture of a medicament for the treatment of such a condition.

The compounds of the present invention may be used alone or in combination with other therapeutic agents. When used in combination with another
10 therapeutic agent the administration of the two agents may be simultaneous or sequential. Simultaneous administration includes the administration of a single dosage form that comprises both agents and the administration of the two agents in separate dosage forms at substantially the same time. Sequential administration includes the administration of the two agents according to
15 different schedules provided that there is an overlap in the periods during which the treatment is provided. Suitable agents with which the compounds of formula (I) can be co-administered include aspirin, angiotensin II receptor antagonists (such as losartan, candesartan, telmisartan, valsartan, irbesartan and eprosartan), calcium channel blockers (such as amlodipine), beta-blockers (i.e.
20 beta-adrenergic receptor antagonists such as sotalol, propranolol, timolol, atenolol, carvedilol and metoprolol), C1027, CCR5 receptor antagonists, imidazolines, sGCa's (soluble guanylate cyclase activators) antihypertensive agents, diuretics (such as hydrochlorothiazide, torsemide, chlorothiazide, chlorthalidone and amiloride), alpha adrenergic antagonists (such as doxazosin),
25 ACE (angiotensin converting enzyme) inhibitors (such as quinapril, enalapril, ramipril and lisinopril), aldosterone receptor antagonists (such as eplerenone and spironolactone), neutral endopeptidase inhibitors, antidiabetic agents (such as insulin, sulfonylureas (such as glyburide, glipizide and glimepiride), glitazones (such as rosiglitazone and pioglitazone) and metformin), cholesterol lowering
30 agents (such as atorvastatin, pravastatin, lovastatin, simvastatin, clofibrate and rosuvastatin), and alpha-2-delta ligands (such as gabapentin, pregabalin, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-

ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1 α ,3 α ,5 α)-(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-amino-5-methyl-octanoic acid).

The compounds of formula (I) may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

-32-

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, 5 intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

10 Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

15 The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

20 The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

25 Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

30

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting

powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1 µg to 10mg of the compound of the invention per actuation and the actuation volume may vary from 1 µl to 100 µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-co-glycolic acid) (PLGA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with

the invention are typically arranged to administer a metered dose or "puff" containing from 1 µg to 20mg of the compound of formula (I). The overall daily dose will typically be in the range 1 µg to 80mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

5

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

10

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

15

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers,

20

lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelatin gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

25

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

30

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene

glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

- 5 Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and
- 10 gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

- Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is
- 15 within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

- 20 Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula ... in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of
- 25 tablets, capsules and the like.

- The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate
- 30 compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.1mg to 500mg depending, of course, on the mode of administration. For example, oral administration may require a total daily dose of from 0.1mg to 500mg, while an intravenous dose may only require
5 from 0.01mg to 50mg. The total daily dose may be administered in single or divided doses.

These dosages are based on an average human subject having a weight of about 65kg to 70kg. The physician will readily be able to determine doses for
10 subjects whose weight falls outside this range, such as infants and the elderly.

Compounds of the invention may be prepared, in known manner in a variety of ways. In the following reaction schemes and hereafter, unless otherwise stated R^1 to R^6 are as defined in the first aspect. These processes form further aspects of
15 the invention.

a) Compounds of formula (I) can be prepared from the corresponding monochlorides of formula (II) by reaction with HNR^3R^4 as illustrated in Scheme
1.

20

Scheme 1

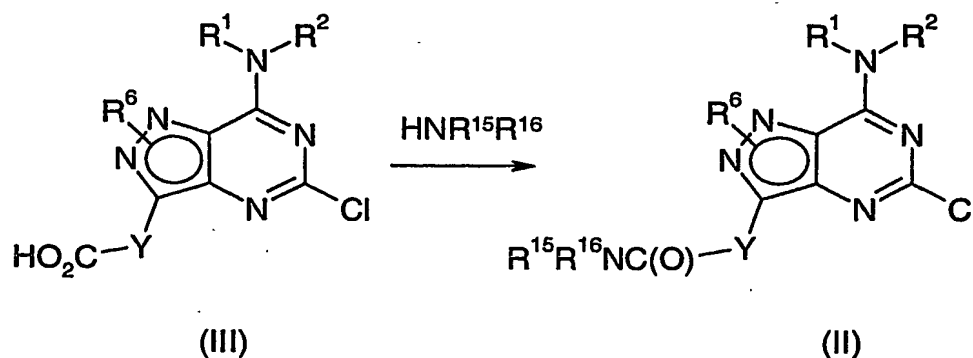
A solution of the monochloride (II) and the amine HNR^3R^4 in a suitable dipolar aprotic solvent are stirred at elevated temperature for between 1 and 24 hours.
25 Suitable solvents include dimethylsulfoxide, dimethylformamide and N-methylpyrrolidinone. An excess of a tertiary amine such as N-ethyl-diisopropylamine, N-methylmorpholine or triethylamine, and/or a fluoride source such as caesium fluoride or tetraethylammonium fluoride may optionally

be included. It is sometimes necessary to perform the reaction at elevated pressure in a closed vessel, particularly when the amine HNR^3R^4 or the solvent is volatile.

- 5 Preferably, the monochloride is treated with 3-5 equivalents of the amine HNR^3R^4 and 3-5 equivalents of N-ethyldiisopropylamine in dimethylsulfoxide or N-methylpyrrolidinone, optionally in the presence of caesium fluoride or tetraethylammonium fluoride, at 80-125°C for 12-18 hours.
- 10 It will be appreciated that any functional groups in HNR^3R^4 , and particularly any primary or secondary amine groups, may need to be protected in order to allow this reaction to proceed successfully. In such a case, or when there is a functional group in another part of the structure of (I) that is protected, such as an amine group in R^1 or R^5 , the final step of the synthesis will be a deprotection
- 15 step. For example, if there is an amine group protected by a BOC group, then treatment with acid (such as hydrogen chloride in dioxan or trifluoroacetic acid) will be used. If benzyloxycarbonyl is the preferred amine protecting group, the unmasking step can be a hydrogenolysis. Similarly, any carboxylic acids protected as esters can be deprotected by appropriate methods, such as
- 20 treatment with trifluoroacetic acid (for *tert*-butyl esters) or hydrogenolysis (for benzyl esters).

b) Compounds of formula (II) can be prepared from the corresponding acids of formula (III) by reaction with $\text{HNR}^{15}\text{R}^{16}$ as illustrated in Scheme 2.

25

Scheme 2

A solution of the acid (III) and the amine $\text{HNR}^{15}\text{R}^{16}$ in a suitable solvent is treated with a condensing agent, optionally in the presence of 1-hydroxy-benzotriazole (HOBT) (or 1-hydroxy-7-azabenzotriazole (HOAT)) and a tertiary amine base such as triethylamine, N-ethyl-diisopropylamine or 4-(dimethylamino)pyridine, at a temperature of between 0°C and the boiling point of the solvent. Suitable solvents include acetonitrile, dichloromethane, dimethylformamide, ethyl acetate, N-methylpyrrolidinone, tetrahydrofuran and mixtures thereof. Suitable condensing agents include: 1,1'-carbonyldiimidazole, carbodiimides such as dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-1-ethylcarbodiimide (WSCDI); uronium salts such as O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU); phosphonium salts such as 1-benzotriazolyloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) and 1-benzotriazolyloxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP); diphenylphosphinic chloride (Dpp-Cl) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl).

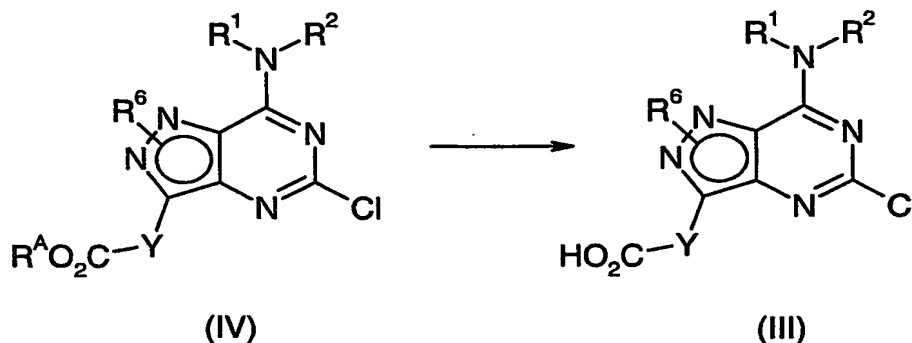
Alternatively the acid may be converted to a more reactive derivative such as the acid chloride, for example by treatment with thionyl chloride or oxalyl chloride.

The reactive derivative is then reacted with the amine $\text{HNR}^{15}\text{R}^{16}$ in a suitable solvent, in the presence of a tertiary amine base such as triethylamine, N-ethyl-diisopropylamine or 4-(dimethylamino)pyridine. Suitable solvents include dichloromethane and dimethylformamide.

The transformations of Schemes 2 and 1 may conveniently be carried out sequentially without isolation of the intermediate of formula (II). Thus the compounds of formula (III) may be treated with an amine $\text{HNR}^{15}\text{R}^{16}$ at room temperature in the presence of 1,1'-carbonyldiimidazole, then a second amine HNR^3R^4 may be added and the mixture heated to 120°C so as to provide the compounds of formula (I) directly.

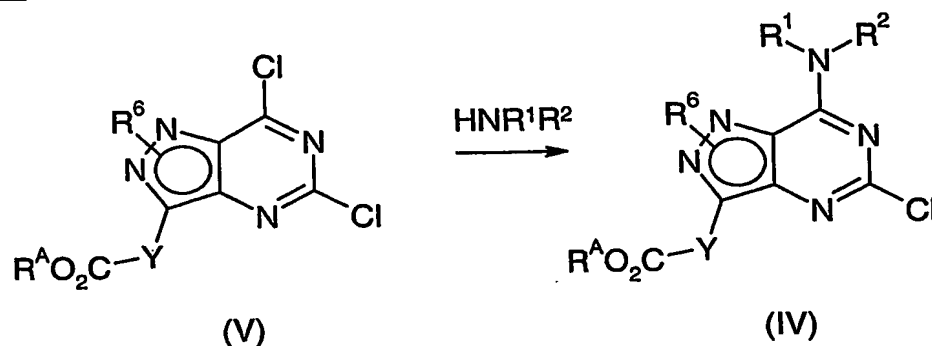
c) Compounds of formula (III) can be prepared from the corresponding esters of formula (IV) wherein R^A is an alkyl group (particularly a methyl, ethyl, or *tert*-butyl group) or a benzyl group, as illustrated in Scheme 3.

5 Scheme 3



When R^A is methyl or ethyl the conversion may conveniently be accomplished by treating the compound of formula (IV) with an alkaline metal hydroxide such as lithium, sodium or potassium hydroxide in a suitable solvent at a temperature of between about 10°C and the boiling point of the solvent. Suitable solvents include water, methanol, ethanol and mixtures of water with methanol, ethanol, tetrahydrofuran and dioxan. When R^A is *tert*-butyl the conversion may be accomplished by treating the compound of formula (IV) with an acid such as hydrogen chloride or trifluoroacetic acid in a suitable solvent at a temperature of between 0°C and ambient temperature. Suitable solvents include dioxan and dichloromethane. When R^A is benzyl the conversion may conveniently be accomplished by treating the compound of formula (IV) with an alkaline metal hydroxide as discussed above, or by hydrogenolysis using molecular hydrogen or a suitable hydrogen donor such as ammonium formate in the presence of a transition metal or transition metal salt catalyst such as palladium-on-carbon, in a suitable solvent, such as methanol.

d) Compounds of formula (IV) can generally be prepared from the corresponding dichlorides of formula (V) by reaction with HNR^1R^2 as illustrated in Scheme 4.

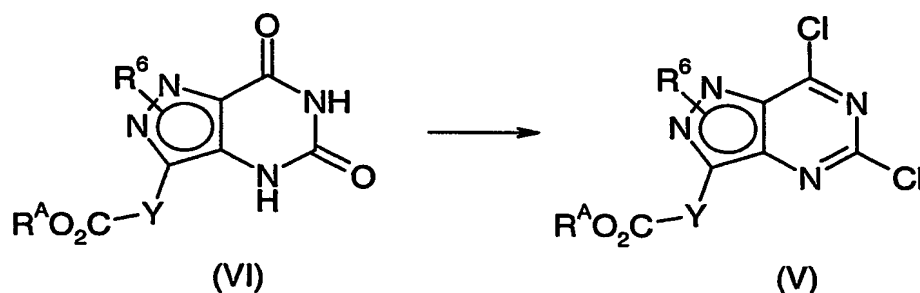
Scheme 4

A solution of the dichloride (V), the amine HNR¹R² and an excess of a tertiary amine such as N-ethyldiisopropylamine, N-methylmorpholine or triethylamine in a suitable dipolar aprotic solvent are stirred at ambient or elevated temperature for between 1 and 24 hours. Suitable solvents include dichloromethane, dimethylsulfoxide, dimethylformamide, tetrahydrofuran and N-methylpyrrolidinone. It will be appreciated that any functional groups in HNR¹R², and particularly any primary or secondary amine groups, may need to be protected in order to allow this reaction to proceed successfully. Preferably, the monochloride is treated with 3-5 equivalents of the amine HNR¹R² and optionally 3-5 equivalents of N-ethyldiisopropylamine in dimethylsulfoxide or a mixture of dimethylsulfoxide and N-methylpyrrolidinone at 30-90°C for 1-18 hours.

Alternatively, a solution of the amine HNR¹R² in a suitable solvent is treated with butyllithium or sodium hexamethyldisilazide at low temperature, and the dichloride is added to the resulting solution. Suitable solvents include tetrahydrofuran, dioxan and N-methylpyrrolidinone.

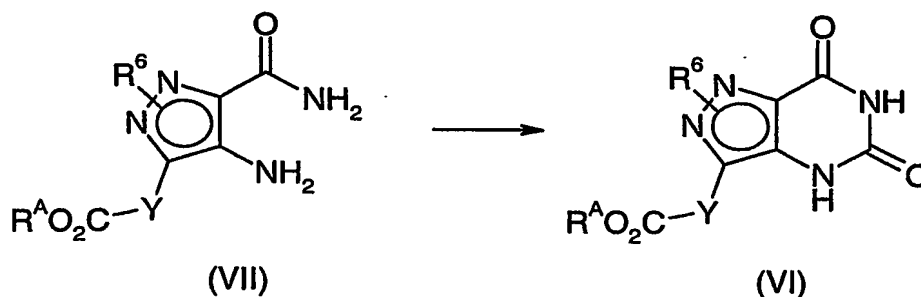
In certain cases, particularly when Y is a covalent bond and the amine HNR¹R² is only weakly nucleophilic, the direct transformation of compounds of formula (V) into compounds of formula (IV) gives unsatisfactory results and a more indirect alternative route may be employed. This route is discussed in part z) below.

e) Compounds of formula (V) can be prepared from the corresponding pyrazolopyrimidinediones formula (VI) as illustrated in Scheme 5.

Scheme 5

- 5 The dione is treated with a large excess of a suitable chlorinating reagent such as phosphorus oxychloride (POCl_3) or phenylphosphonyl dichloride ($\text{PhP}(\text{O})\text{Cl}_2$) in the presence of a tertiary amine such as N-ethyldiisopropylamine, N-methylmorpholine, triethylamine or N,N-dimethylaniline at elevated temperature for 8-48 hours. Dimethylformamide can optionally be added as a catalyst.
- 10 Alternatively, the dione is treated with POCl_3 or $\text{PhP}(\text{O})\text{Cl}_2$ in a suitable solvent in the presence of a tetraalkylammonium chloride, such as tetraethylammonium chloride, at elevated temperature. Suitable solvents include acetonitrile and propionitrile. Preferably, the dione is treated with 10-30 equivalents of POCl_3 and 3-5 equivalents of tetraethylammonium chloride in propionitrile at reflux for
- 15 4-18 hours.

f) Compounds of formula (VI) can be prepared from the corresponding aminoamides of formula (VII) as illustrated in Scheme 6.

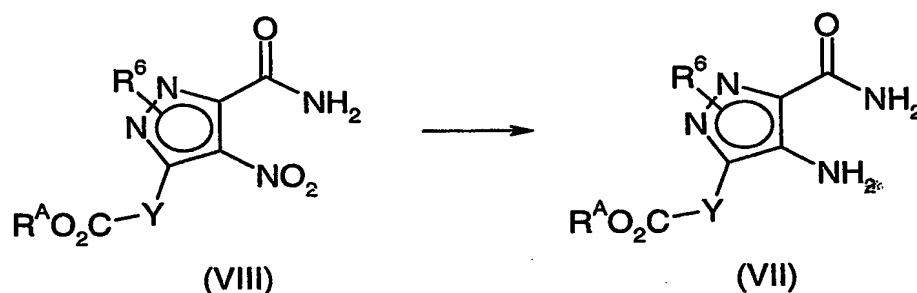
20 Scheme 6

A solution of the pyrazolecarboxamide (VII) and phosgene or an equivalent thereof, such as 1,1'-carbonyldiimidazole, trichloromethyl chloroformate or bis(trichloromethyl) carbonate, in a suitable solvent is stirred at a temperature of

between ambient temperature and the boiling point of the solvent, optionally at elevated pressure, for between 2 and 18 hours. Suitable solvents include acetonitrile, dichloromethane and dimethylformamide. Preferably, a solution of the dione and 1 equivalent of carbonyl diimidazole in dimethylformamide is stirred at 70°C to 90°C for 18 hours.

g) Compounds of formula (VII) can be prepared from the corresponding nitroamides of formula (VIII) as illustrated in Scheme 7.

10 Scheme 7



Reduction of the nitro group can be achieved by, for example, transfer or catalytic hydrogenation, or by a dissolving metal reduction.

15 For transfer hydrogenation, the nitro compound is reacted with a suitable hydrogen donor, such as ammonium formate or cyclohexene, in a polar solvent, such as tetrahydrofuran, methanol or ethanol, in the presence of a transition metal or transition metal salt catalyst, such as palladium or palladium(II) hydroxide, optionally at elevated temperature and pressure.

20

For catalytic hydrogenation, a solution of the nitro compound in a polar solvent, such as tetrahydrofuran, methanol or ethanol, is stirred under a hydrogen atmosphere in the presence of a transition metal or transition metal salt catalyst, such as palladium or palladium(II) hydroxide, optionally at elevated pressure.

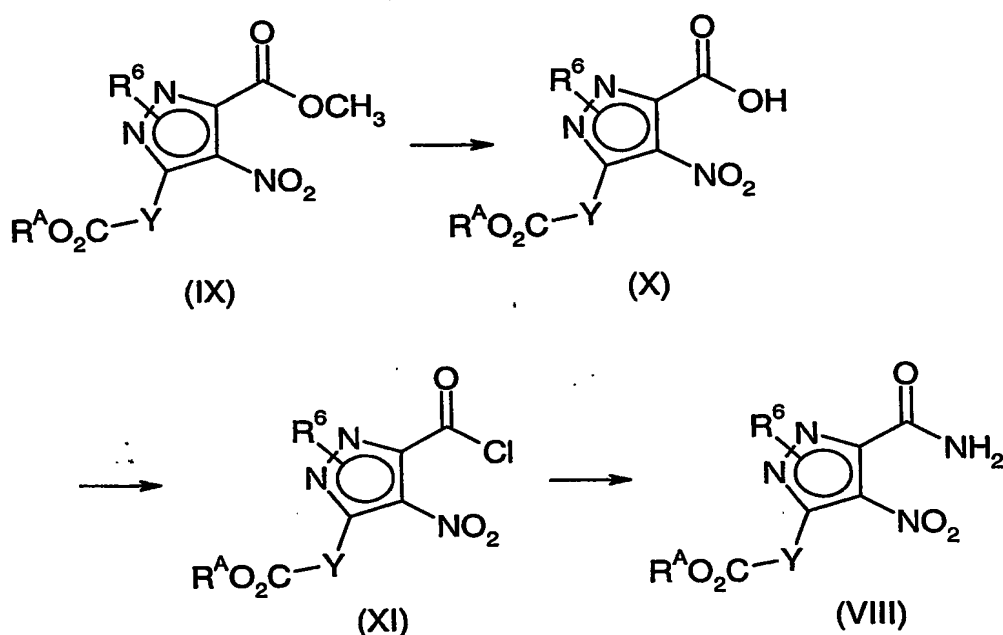
25 The catalyst may be in solution (homogeneous catalysis) or in suspension (heterogeneous catalysis).

For dissolving metal reduction, the nitro compound is treated with a suitable reactive metal, such as zinc or tin, in the presence of an acid such as acetic acid or hydrochloric acid. Other reducing agents, such as tin(II) chloride, may also be used.

5

h) Compounds of formula (VIII) can be prepared from the corresponding nitroesters of formula (IX) as illustrated in Scheme 8.

Scheme 8



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The methyl ester of the compounds of formula (IX) can be hydrolysed under basic conditions as described in part c) above. For some embodiments of Y, the choice of R^A will be limited to those that form esters that are resistant to alkaline hydrolysis, such as branched alkyl groups. The acid (X) is then

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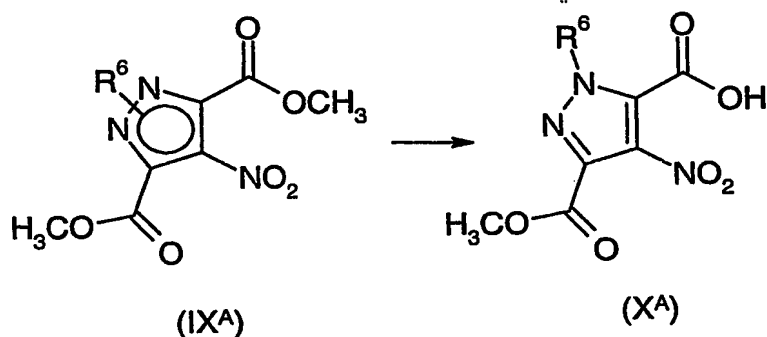
converted to the corresponding acid chloride (XI) by treatment with oxalyl chloride and dimethylformamide in a suitable solvent such as dichloromethane, or with thionyl chloride. Finally, a solution of the acid chloride in a suitable solvent such as dichloromethane, tetrahydrofuran or dioxan is treated with gaseous ammonia or aqueous ammonia to provide the amide of formula (VIII).

20

In the embodiments (IX^A) in which Y is a covalent bond and R^A is a methyl group, the use of one equivalent of metal hydroxide leads to the chemoselective

hydrolysis of the ester group adjacent to the R^6 substituent (Chambers, D *et al.*, J. Org. Chem. 50, 4736-4738, 1985), as illustrated in Scheme 8A.

Scheme 8A

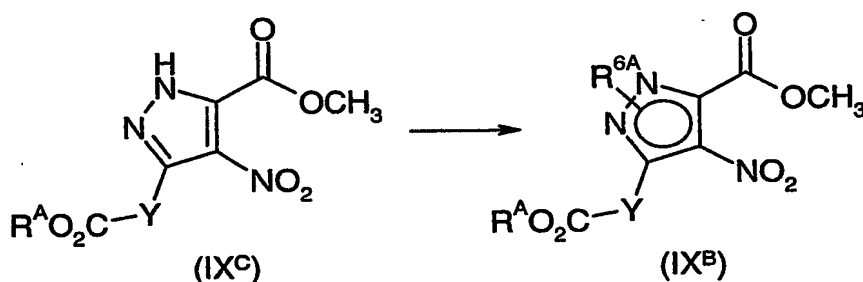


5

- i) Compounds of formula (IX^B), wherein R^{6A} is any group according to R^6 except hydrogen, i.e. compounds of formula (IX) except those wherein R^6 is hydrogen, can be prepared from the corresponding esters of formula (IX^C), i.e. compounds of formula (IX) wherein R^6 is hydrogen, as illustrated in Scheme 9.

10

Scheme 9



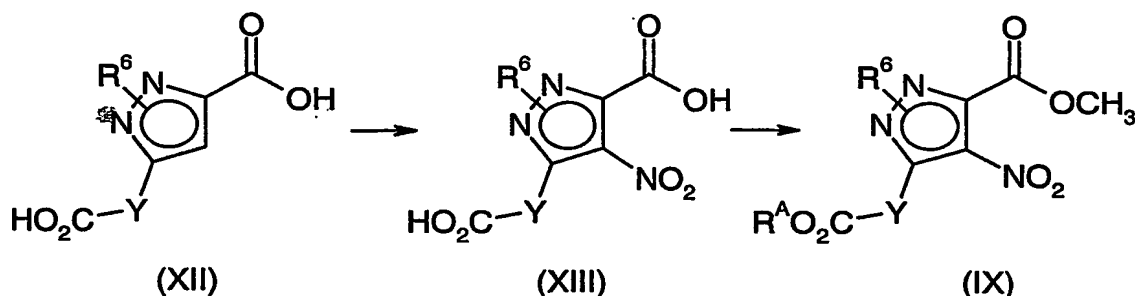
- 15 The compound of formula (IX^C) is treated with a base such as an alkaline metal carbonate or bicarbonate, for example potassium carbonate or caesium carbonate, or a tertiary amine, for example triethylamine, diisopropylethylamine or pyridine, and the appropriate chloride ($R^{6A}-\text{Cl}$), bromide ($R^{6A}-\text{Br}$), iodide ($R^{6A}-\text{I}$), mesylate ($R^{6A}-\text{OSO}_2\text{CH}_3$) or tosylate ($R^{6A}-\text{OSO}_2\text{Tol}$) in a suitable solvent at a temperature of between -70°C and 100°C . Suitable solvents include ethers
- 20 such as tetrahydrofuran and dioxan, dimethylformamide and acetonitrile. Stronger bases such as sodium hydride, potassium *tert*-butoxide and sodium or potassium hexamethyldisilazide may also be used. Alternatively, the transformation may be achieved using the Mitsunobu reaction, in which a

solution of the compound of formula (IX^C) and the appropriate alcohol R^{6A}-OH in a suitable solvent is treated with triphenylphosphine and a dialkyl azodicarboxylate such as diethyl azodicarboxylate or diisopropyl azodicarboxylate. A preferred solvent is tetrahydrofuran. The reaction is performed at a temperature of between -10°C and ambient temperature.

When the reaction gives a mixture of the N¹- and N²-alkylated products, these can be separated using standard techniques.

- j) The compound of formula (IX^C) wherein R^A is methyl and Y is a covalent bond is described in published international patent application WO00/24745 (see preparation 2, page 48). Other compounds of formula (IX), and particularly compounds of formula (IX^C), can be prepared in two steps from the diacids of formula (XII), as illustrated in Scheme 10.

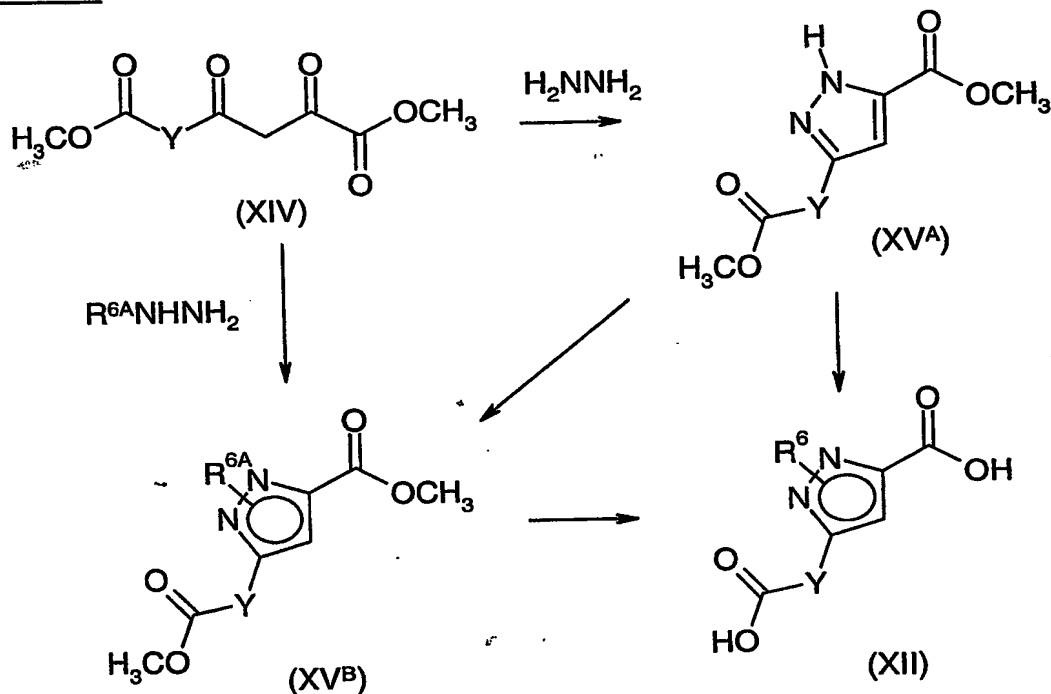
Scheme 10



In the first step, the compounds of formula (XII) are treated with a nitrating agent such as nitric acid or a mixture of nitric acid and sulphuric acid to provide the compounds of formula (XIII). In the second step, the two carboxylic acid groups are esterified. When R^A is methyl, this is conveniently achieved in a single operation. When R^A is other than methyl, two sub-steps are necessary, and the order in which the two groups are esterified will depend on the nature of Y and R⁶. Suitable conditions for forming esters are well known in the art. When R^A is methyl, a preferred method is to treat the diacid with thionyl chloride so as to form the bis-chloride and then react this with methanol.

k) Certain compounds of formula (XII) are commercially available or are described in the literature, in particular those wherein Y is a covalent bond. Compounds of formula (XII) that are not items of commerce can be prepared as illustrated in Schemes 11 to 13, in which R^A is as defined in part j) above.

5

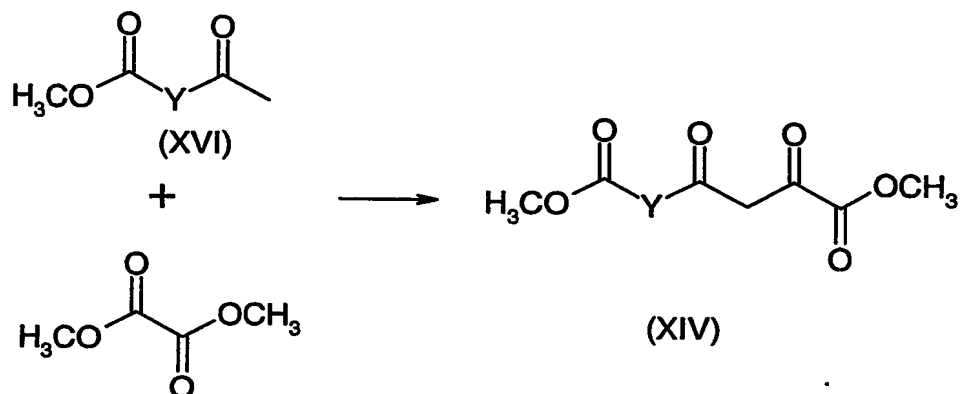
Scheme 11

The method illustrated in Scheme 11 is the Knorr pyrazole synthesis. A 1,3-diketone of formula (XIV) is reacted with hydrazine to give a pyrazole of formula (XV^A), or with a substituted hydrazine $R^{6A}-NHNH_2$ to give a pyrazole of formula (XV^B).

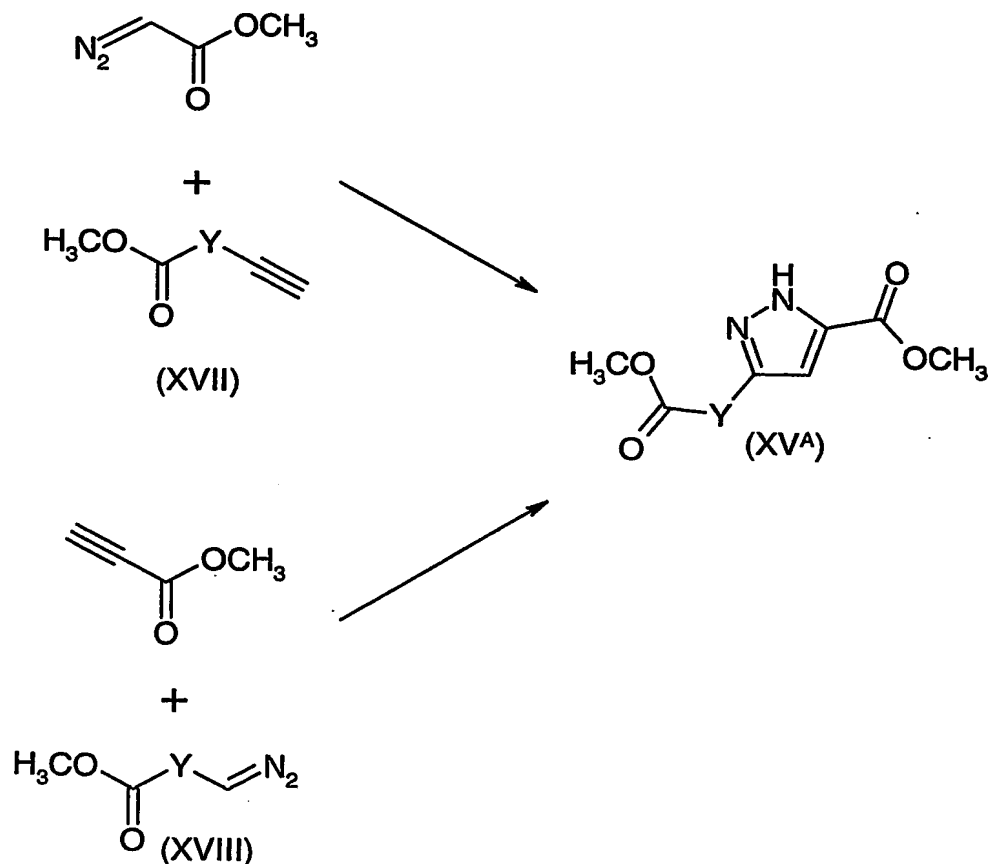
Pyrazoles of formula (XV^B) may also be obtained by N-alkylation of the corresponding pyrazoles of formula (XV^A) following the methods described in part i) above. Hydrolysis of the ester groups as described in part c) above then provides the compounds of formula (XII).

Compounds of formula (XIV) can be prepared from the corresponding methyl ketones of formula (XVI) using a crossed Claisen condensation as illustrated in Scheme 12.

20

Scheme 12

A methyl ketone of formula (XVI) is reacted with dimethyl oxalate in a suitable solvent in the presence of a suitable base. Suitable solvents include ethers, such as tetrahydrofuran. Suitable bases include sodium hydride, potassium *tert*-butoxide and lithium diisopropylamide. Alternatively, sodium methoxide may be used as the base and methanol as the solvent.

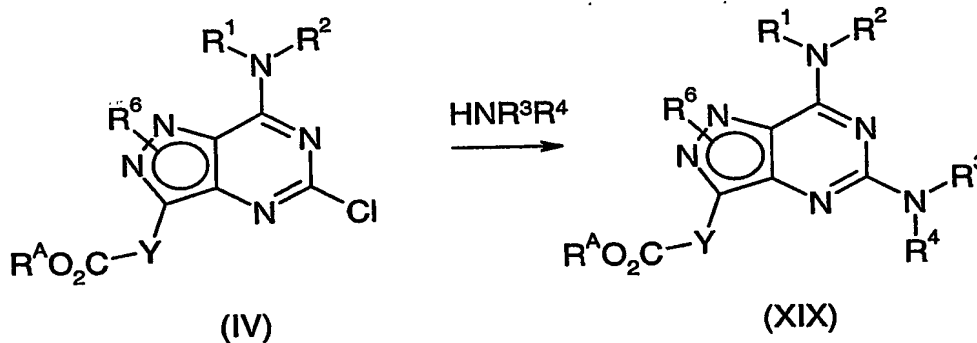
Scheme 13

The method illustrated in Scheme 13 is the Pechmann pyrazole synthesis. A diazo compound and an acetylene are combined to produce a pyrazole of formula (XV^A). When Y is other than a covalent bond two variants of the method can be considered. An acetylene of formula (XVII) can be combined with methyl diazoacetate, or a diazo compound of formula (XVIII) can be combined with methyl propiolate. The initial reaction product (XV^A) may be carried forward as described above.

As an alternative to the steps described in parts a) to c) above, compounds of formula (IV) may be elaborated to give compounds of formula (I) by the following method.

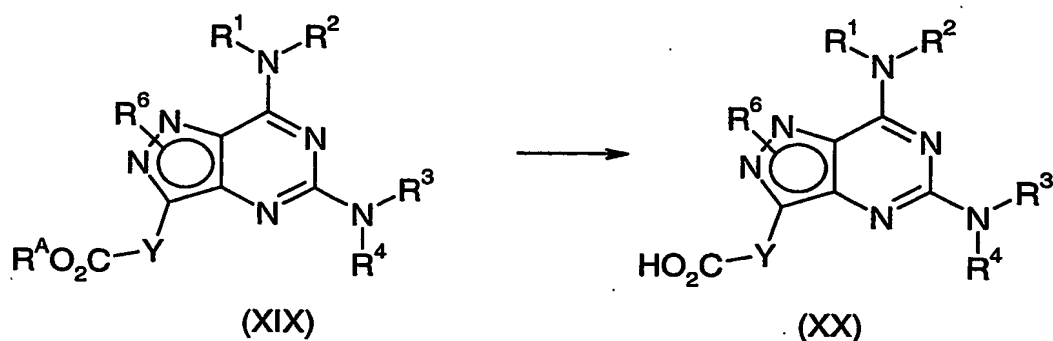
l) The monochlorides of formula (IV) can be converted to diamines of formula (XIX) as illustrated in Scheme 14.

Scheme 14



The transformation can be achieved using the methods described in part a) above.

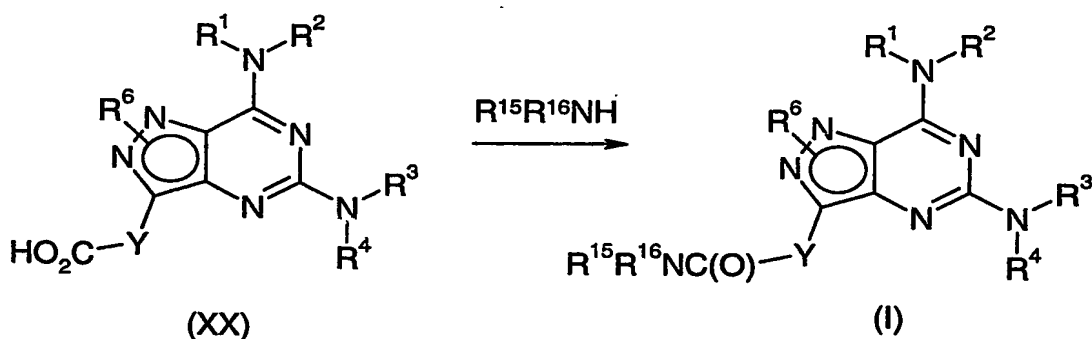
m) The esters of formula (XIX) can be converted to acids of formula (XX) as illustrated in Scheme 15.

Scheme 15

The transformation can be achieved using the methods described in part c) above.

5

n) The acids of formula (XX) can be converted to compounds of formula (I) as illustrated in Scheme 16.

Scheme 16

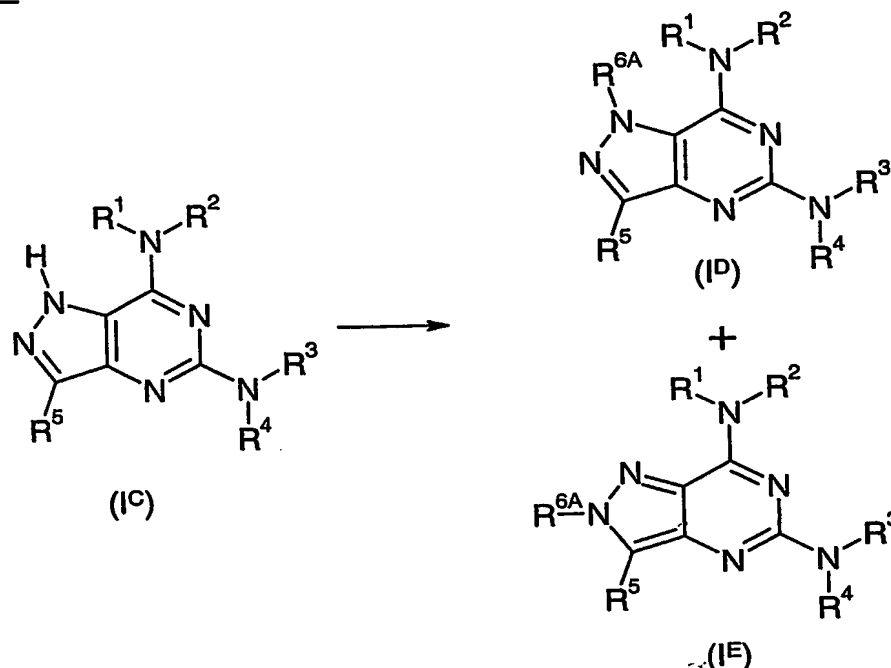
10

The transformation can be achieved using the methods described in part b) above.

o) In some embodiments of the compounds of formula (I), the group R^6 may not be compatible with the synthetic methods described above. An alternative in these circumstances is to introduce the R^6 group at a late stage, as illustrated in Scheme 17.

15

Scheme 17



A compound of formula (I^C), i.e. a compound of formula (I) wherein R⁶ is hydrogen, can be alkylated using the methods described in part j) above. The reaction will generally give a mixture of the N¹-alkylated compound (I^D) and the N²-isomer (I^E). These can be separated and purified by conventional methods. The use of more reactive alkylating agents tends to promote alkylation at the N² position.

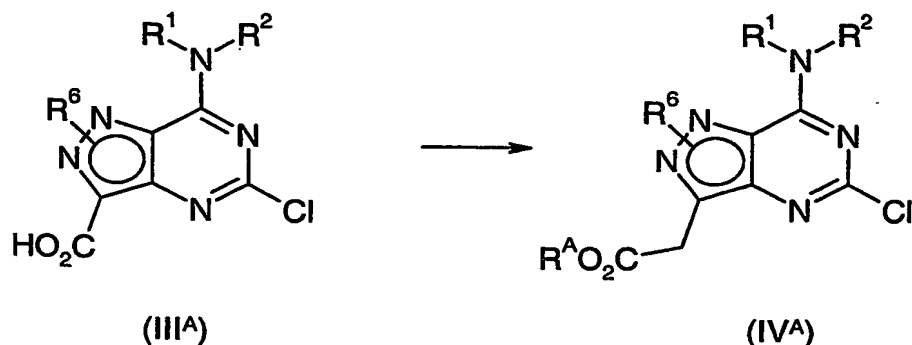
It will be appreciated that the alkylation reaction to introduce R^{6A} might also be carried out at other stages in the synthetic sequence.

In addition to the methods described above, certain compounds of general formulae (III) and (IV) may be prepared by elaboration of the substituent at the C³ position of the pyrazolopyrimidine, as further illustrated below. It will be appreciated that the synthetic transformations discussed may also be used in the elaboration of the C³-substituent of compounds at any other stage of the synthetic sequence.

p) Compounds of formula (IV^A), i.e compounds of formula (IV) wherein Y is CH₂, may be prepared from the corresponding compounds of formula (III^A), i.e.

compounds of formula (III) wherein Y is a covalent bond, by a one-carbon homologation method such as the Arndt-Eistert reaction illustrated in Scheme 18.

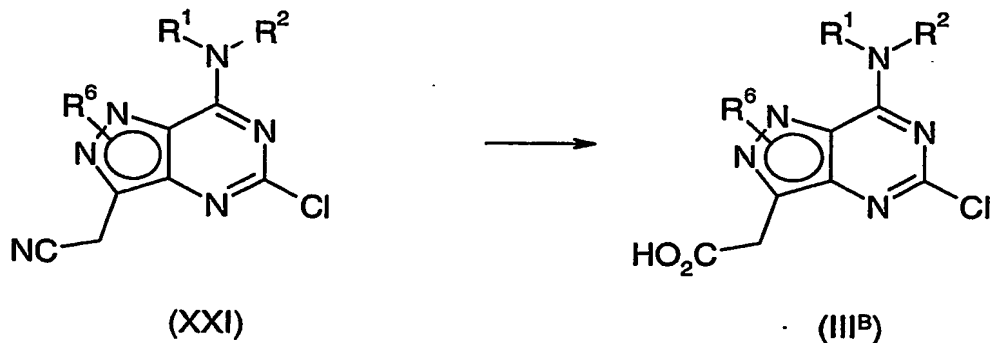
5 Scheme 18



The carboxylic acid is converted to a reactive intermediate such as the acid chloride (by reaction with oxalyl chloride) or a mixed anhydride (by reaction with isobutyl chloroformate). The intermediate is reacted with diazomethane to provide an α -diazoketone. This is treated with silver oxide in the presence of R^A-OH to give the homologated ester of formula (IV^A).

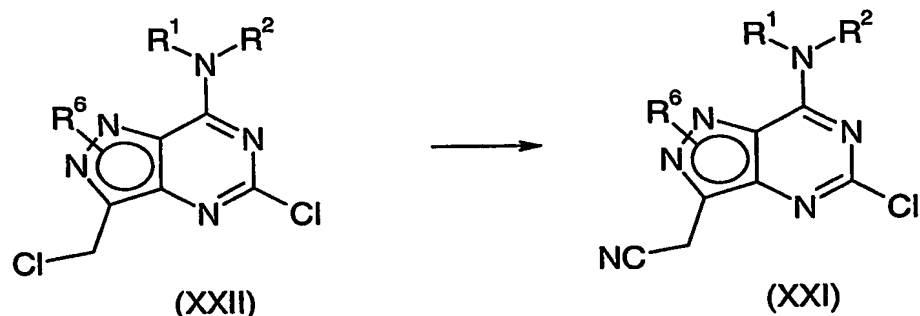
q) Compounds of formula (III^B), i.e. compounds of formula (III) wherein Y is CH₂, may be prepared from the corresponding nitriles of formula (XXI) by the method illustrated in Scheme 19.

Scheme 19



The nitrile can be hydrolysed by treatment with aqueous mineral acids, such as hydrochloric acid, optionally at elevated temperature.

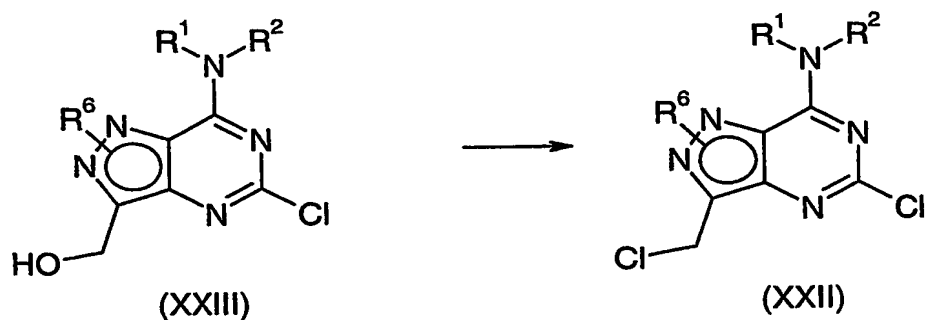
- r) Compounds of formula (XXI) can be prepared from the corresponding chlorides of formula (XXII) by the method illustrated in Scheme 20.

Scheme 20

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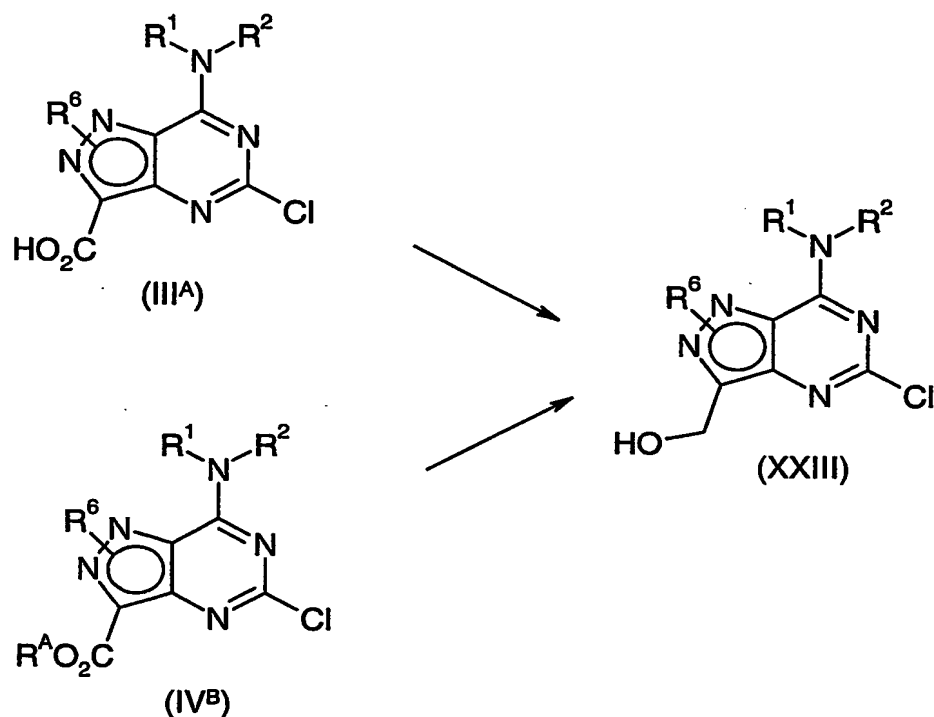
The chloride is treated with a metal cyanide, such as sodium cyanide or potassium cyanide in a suitable solvent, such as dimethylsulfoxide, dimethylformamide or ethanol.

- 10 s) Compounds of formula (XXII) can be prepared from the corresponding alcohols of formula (XXIII) by the method illustrated in Scheme 21.

Scheme 21

- 15 The alcohol is treated with thionyl chloride or with a mixture of triphenylphosphine and either *N*-chlorosuccinimide or tetrachloromethane.

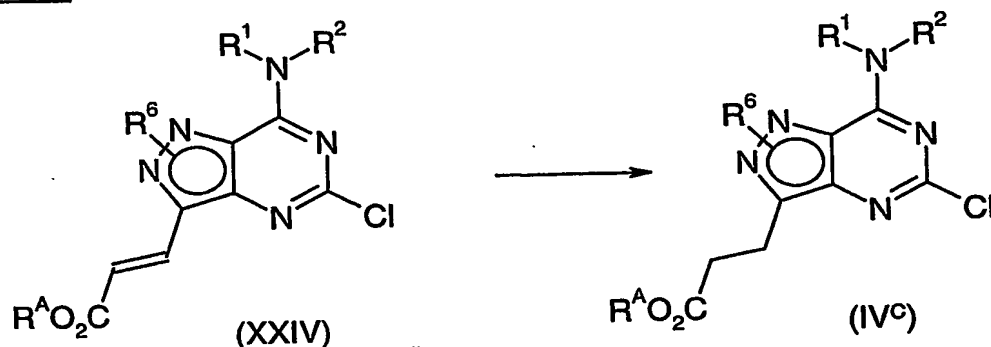
- t) Compounds of formula (XXIII) can be prepared from the corresponding esters of formula (IV^B), i.e. compounds according to formula (IV) wherein Y is a covalent bond, or from the corresponding acids of formula (III^A) by the method illustrated in Scheme 22.
- 20

Scheme 22

The acids of formula (III^A) and the esters of formula (IV^B) can be reduced to the alcohols of formula (XXIII) by treatment with lithium aluminium hydride in a suitable solvent at a temperature of between 0° and the boiling point of the solvent. Suitable solvents include ethers such as tetrahydrofuran. The acids can also be reduced by treatment with isobutyl chloroformate and a tertiary amine base to provide a mixed anhydride, followed by reaction with sodium borohydride. The esters can also be reduced by treatment with diisobutylaluminium hydride or lithium borohydride.

u) Compounds of formula (IV^C), i.e. compounds of formula (IV) wherein Y is CH₂CH₂, can be prepared from the corresponding acrylate ester of formula (XXIV) by the method illustrated in Scheme 23.

Scheme 23



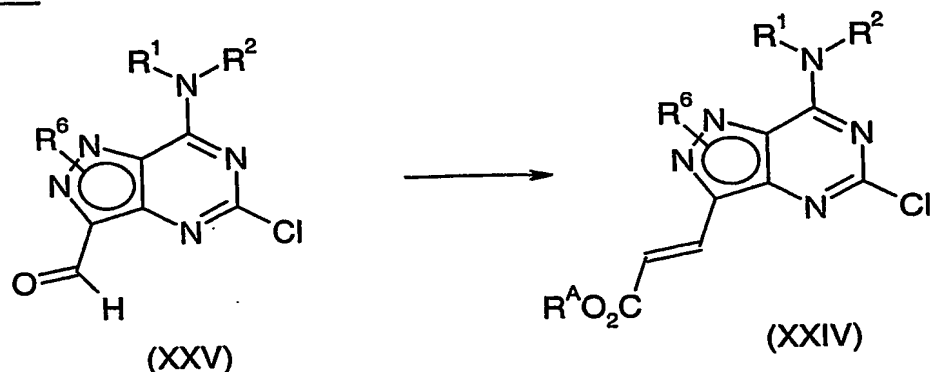
The reduction of the carbon-carbon double bond of (XXIV) to give the compounds of formula (IV^C) can be accomplished by catalytic hydrogenation using molecular hydrogen in the presence of a transition metal catalyst such as palladium, platinum or nickel. When R^A is benzyl the conditions can be chosen such that only the double bond is reduced or reduction is accompanied by hydrogenolytic cleavage of the ester to give the carboxylic acid.

10 The acrylates of formula (XXIV) can also be treated with alkylcopper reagents to give analogues of the compounds of formula (IV^C) in which an alkyl substituent is introduced on the carbon atom adjacent to the pyrazolopyrimidine ring system, or with a sulphonium ylid or a carbene equivalent to give a 2-(pyrazolopyrimidinyl)-cyclopropane-1-carboxylate derivative.

15

v) Compounds of formula (XXIV) can be prepared from the corresponding aldehydes of formula (XXV) by the method illustrated in Scheme 24.

Scheme 24

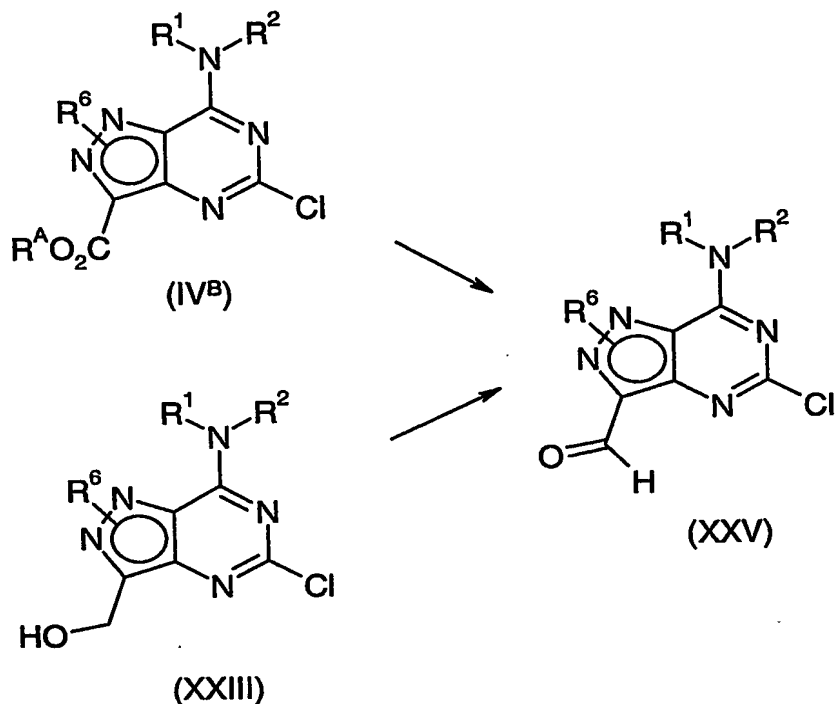


The aldehyde of formula (XXV) can be converted to the acrylate ester of formula (XXIV) by reaction with a phosphorus reagent following the protocols of the Wittig, Horner or Wadsworth-Horner-Emmons reactions. The reagent is prepared by treating a triphenylphosphonium salt $\text{Ph}_3\text{P}^+\text{CH}_2\text{CO}_2\text{R}^{\text{A}}.\text{X}^-$ (Wittig), a phosphine oxide $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{R}^{\text{A}}$ (Horner), or a phosphonate $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{R}^{\text{A}}$ (Wadsworth-Horner-Emmons), with a base such as butyllithium, a lithium dialkylamide or an alkaline metal alkoxide, in a suitable solvent such as tetrahydrofuran.

10 The method is not limited to the preparation of α -unsubstituted acrylate esters. The use of an alkyl-substituted phosphorus reagent such as $\text{Ph}_3\text{P}^+\text{CH}(\text{R})\text{CO}_2\text{R}^{\text{A}}.\text{X}^-$ or the equivalent phosphine oxide or phosphonate, wherein R is alkyl, gives access to the corresponding α -alkyl acrylate derivative.

15 The conversion of the aldehydes of formula (XXV) to acrylate esters of formula (XXIV) can also be achieved by reaction with a malonate derivative following the method of the Knoevenagel condensation.

20 w) Compounds of formula (XXV) can be prepared from the esters of formula (IV^{B}) or more preferably from the corresponding alcohols of formula (XXIII) by the methods illustrated in Scheme 25.

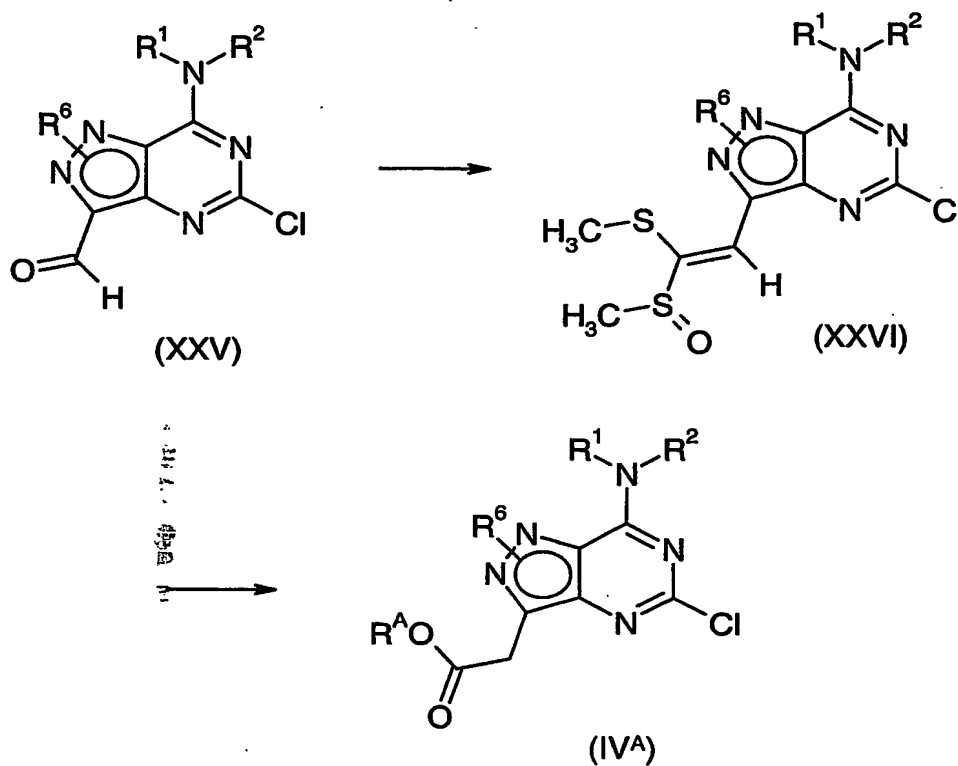
Scheme 25

The reduction of the esters of formula (IV^B) can be achieved using diisobutylaluminium hydride (DIBAL) in a suitable solvent at a temperature of less than 0°C, preferably less than -60°C. Suitable solvents include hydrocarbons such as pentane, hexane and toluene, ethers such as tetrahydrofuran, and mixtures thereof.

The oxidation of the alcohols of formula (XXIII) can be achieved using a chromium(VI) reagent such as pyridinium chlorochromate, a hypervalent iodine reagent such as the Dess-Martin periodinane, or a combination of tetra-n-propylammonium perruthenate and N-methylmorpholine-N-oxide in a suitable solvent at a temperature of between 0°C and ambient temperature. Suitable solvents include dichloromethane.

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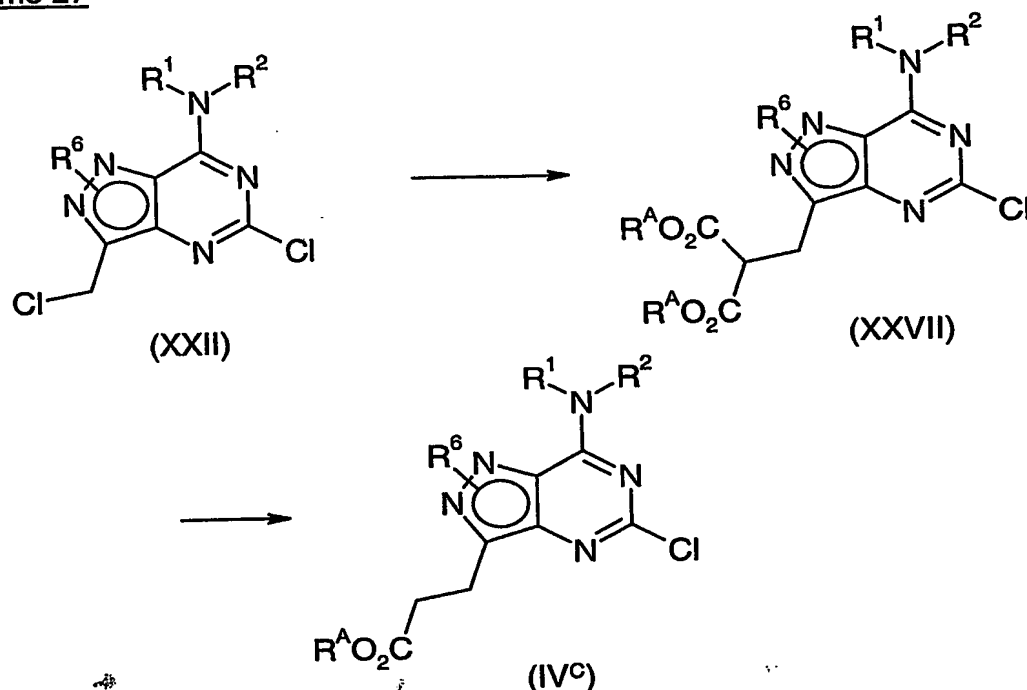
x) The aldehydes of formula (XXV) may be converted to esters of formula (IV^A) as illustrated in Scheme 26

Scheme 26

- The aldehyde is treated with methyl methylmercaptomethyl sulfoxide (CH₃SCH₂S(O)CH₃) and triton B in tetrahydrofuran to give intermediate (XXVI) which is treated with the appropriate alcohol R^AOH and acetyl chloride to provide the ester of formula (IV^A). This method is particularly useful when R^A is methyl.

y) Compounds of formula (IV^C) can also be prepared from the corresponding chlorides of formula (XXII) by the method illustrated in Scheme 27.

Scheme 27



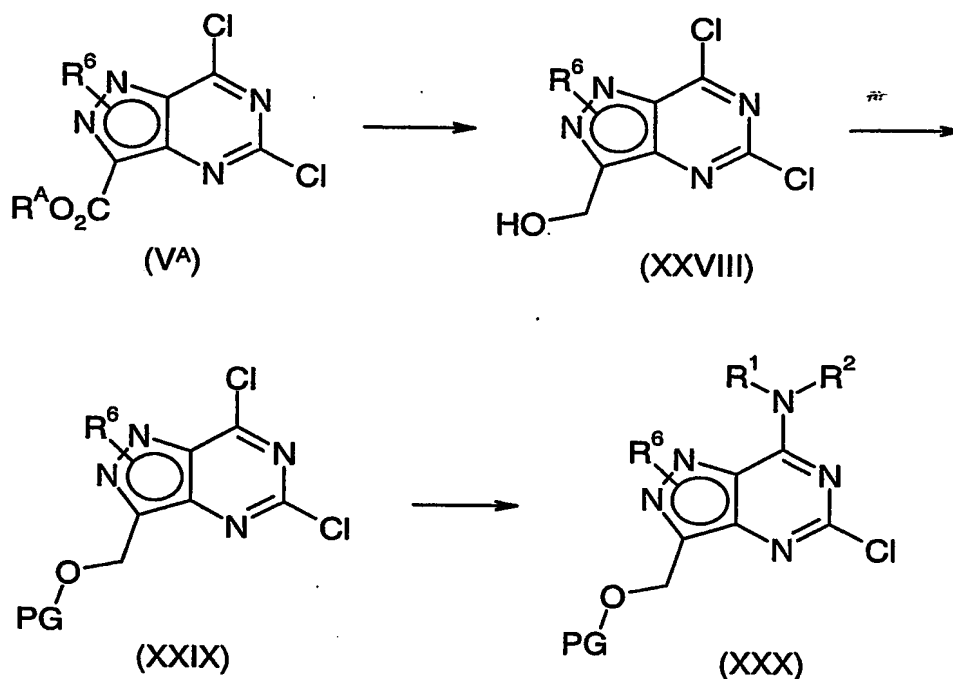
The chloride of formula (XXII) is reacted with a dialkyl malonate ($R^A O_2C$)₂CH₂ and a base in a suitable solvent. Typically, the base is an alkaline metal alkoxide such as sodium ethoxide or potassium *tert*-butoxide, and the solvent is an alcohol such as ethanol or an ether such as tetrahydrofuran. Preferably the base and the solvent are chosen such as to minimise transesterification with the malonate reagent and the intermediate (XXVII). For example, when the reagent is diethyl malonate the base is preferably sodium ethoxide and the solvent is ethanol. The intermediate (XXVII) is then decarboxylated to give the product (IV^C). This can be achieved by selective hydrolysis using one equivalent of an alkaline metal hydroxide, such as sodium hydroxide, followed by acidification, or by any other method known in the art.

The method is not limited to symmetrical malonates. For example, the use of *tert*-butyl methyl malonate would give an intermediate (XXVII) in which one R^A is methyl and the other is *tert*-butyl. By choosing the appropriate conditions, decarboxylation could then be controlled to give a product (IV^C) in which R^A was either *tert*-butyl or methyl.

The method can be extended to substituted malonates ($R^A O_2C$)₂CHR, where R is an alkyl group. This gives access to compounds analogous to (IV^C) in which the group R is a substituent on the carbon atom adjacent to the $R^A O_2C$ group. These compounds can also be prepared by alkylating the intermediate (XXVII) with R-Br or R-I in the presence of an alkaline metal alkoxide base.

z) As mentioned in part d) above, the reaction of compounds of formula (V^A), i.e. compounds of formula (V) wherein Y is a covalent bond, with weakly nucleophilic amines HNR^1R^2 is sometimes not high yielding. An alternative route is illustrated in Schemes 28A and 28B.

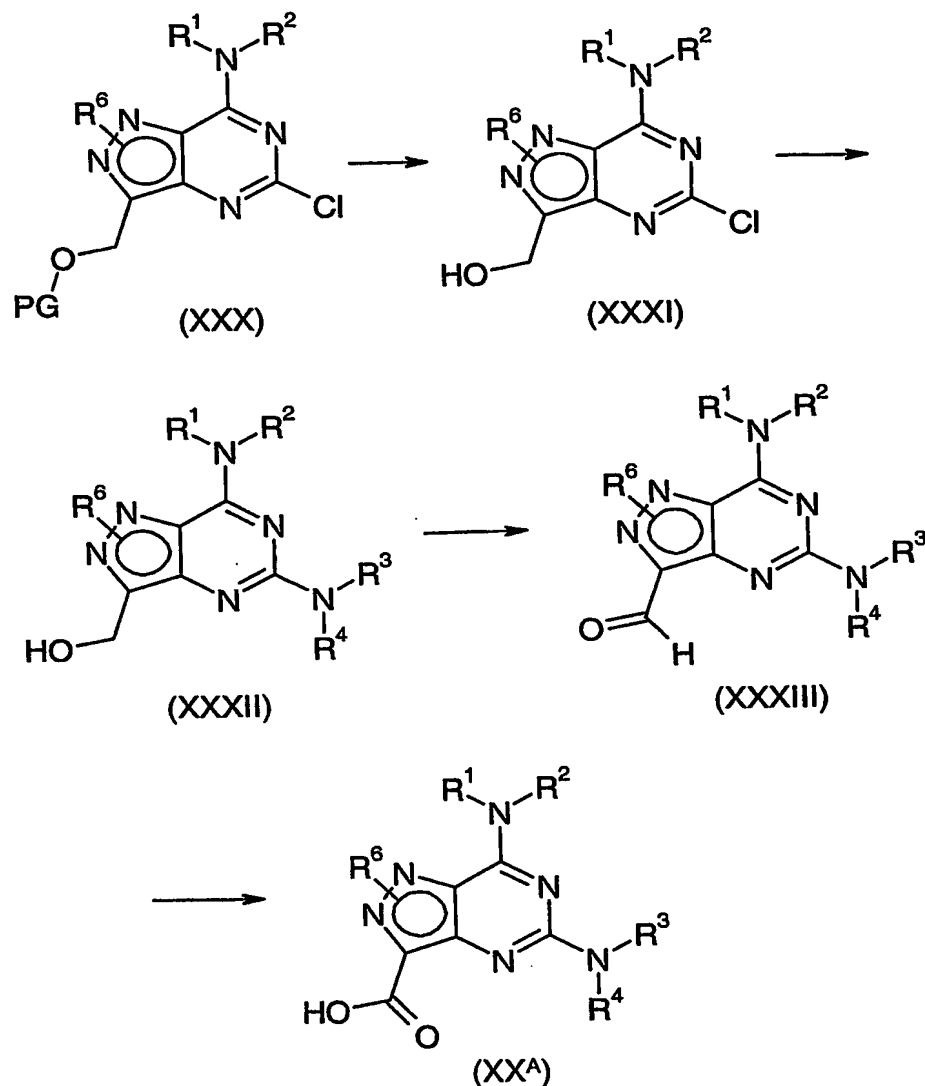
Scheme 28A



The esters of formula (V^A) can be reduced to the alcohols of formula (XXVIII) according to the methods described in part t) above. A preferred method is reduction with diisobutylaluminum hydride at a temperature of between -20°C and 0°C. The primary alcohol is then protected to give compounds of formula (XXIX), wherein PG is an alcohol protecting group. A preferred protecting group is a trialkylsilyl group, particularly a *tert*-butyldimethylsilyl group. The

compounds of formula (XXIX) are then reacted with an amine HNR^1R^2 according to the methods described in part d) above to give compounds of formula (XXX).

Scheme 28B



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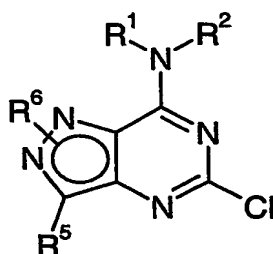
The compounds of formula (XXX) are deprotected to provide the primary alcohols of formula (XXXI) using appropriate conditions. When PG is a trialkylsilyl group it may be removed by treatment with a fluoride salt, such as tetrabutylammonium fluoride. The $-\text{NR}^3\text{R}^4$ group is then introduced according to the methods described in part a) above to provide compounds of formula (XXXII). The primary alcohol is oxidised as described in part w) above to provide the aldehydes of formula (XXXIII). A preferred oxidising agent is the Dess-Martin periodinane. Finally the aldehydes of formula (XXXIII) are oxidised

10

to provide the acids of formula (XX^A), i.e. compounds of formula (XX) wherein Y is a covalent bond. Suitable oxidising agents include potassium permanganate, Jones' reagent and sodium chlorite. A preferred method is to treat the aldehydes with sodium chlorite, sodium dihydrogenphosphate and 2-methyl-2-butene in *tert*-butanol at room temperature for about 1 hour.

The following compounds form further aspects of the present invention:

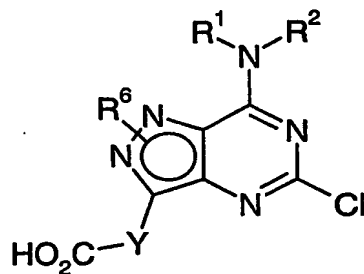
a compound of formula (II)



(II)

wherein R¹, R², R⁵ and R⁶ are as defined above; and

a compound of formula (III)



(III)

wherein R¹, R², R⁶ and Y are as defined above.

The invention is further illustrated by the following, non-limiting examples. Melting points were determined on a Gallenkamp melting point apparatus using glass capillary tubes and are uncorrected. Unless otherwise indicated all

reactions were carried out under a nitrogen atmosphere, using commercially available anhydrous solvents. '0.88 Ammonia' refers to commercially-available aqueous ammonia solution of about 0.88 specific gravity. Thin-layer chromatography was performed on glass-backed pre-coated Merck silica gel (60 F254) plates, and silica gel column chromatography was carried out using 40-63 μ m silica gel (Merck silica gel 60). Ion exchange chromatography was performed using with the specified ion exchange resin which had been pre-washed with deionised water. Proton NMR spectra were measured on a Varian Inova 300, Varian Inova 400, or Varian Mercury 400 spectrometer in the solvents specified. In the NMR spectra, only non-exchangeable protons which appeared distinct from the solvent peaks are reported. Low resolution mass spectra were recorded on either a Fisons Trio 1000, using thermospray positive ionisation, or a Finnigan Navigator, using electrospray positive or negative ionisation. High resolution mass spectra were recorded on a Bruker Apex II FT-MS using electrospray positive ionisation. Combustion analyses were conducted by Exeter Analytical UK. Ltd., Uxbridge, Middlesex. Optical rotations were determined at 25°C using a Perkin Elmer 341 polarimeter using the solvents and concentrations specified. Example compounds designated as (+) or (-) optical isomers are assigned based on the sign of optical rotation when determined in a suitable solvent.

Abbreviations, Definitions and Glossary

| | |
|---------------|--|
| AcOH | acetic acid |
| Amberlyst® 15 | Ion exchange resin, available from Aldrich Chemical Company |
| APCI | Atmospheric Pressure Chemical Ionisation |
| Arbocel™ | Filtration agent, from J. Rettenmaier & Sohne, Germany |
| atm | Pressure in atmospheres (1 atm = 760 Torr = 101.3 kPa) |
| Biotage™ | Chromatography performed using Flash 75 silica gel cartridge, from Biotage, UK |
| BOC | <i>tert</i> -butoxycarbonyl |
| br | Broad |
| c | Concentration used for optical rotation measurements in g per |

| | |
|---|---|
| | 100 ml (1 mg/ml is c 0.10) |
| cat | Catalytic |
| CBz | benzyloxycarbonyl |
| CDI | N,N'-carbonyldiimidazole |
| d | Doublet |
| DCC | N,N'-dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| dd | Doublet of doublets |
| DEAD | diethyl azodicarboxylate |
| Degussa® 101 | 10 wt% palladium on activated carbon, Degussa type E101 available from Aldrich Chemical Company |
| Dess-Martin periodinane | 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one |
| Develosil Combi-RP C ₃₀ hplc column* | Supplied by Phenomenex - manufactured by Nomura Chemical Co. Composed of spherical silica particles (size 3 µm or 5 µm) which have a chemically bonded surface of C30 chains. These particles are packed into stainless steel columns of dimensions 2 cm internal diameter and 25 cm long. |
| DIAD | diisopropyl azodicarboxylate |
| DIBAL | diisobutylaluminium hydride |
| DMAP | 4-dimethylaminopyridine |
| DMF | N,N-dimethylformamide |
| DMSO | dimethyl sulphoxide |
| Dowex® | Ion exchange resin, from Aldrich Chemical Company |
| ee | Enantiomeric excess |
| Et ₃ N | triethylamine |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| HOAT | 1-hydroxy-7-azabenzotriazole |
| HOBT | 1-hydroxybenzotriazole hydrate |
| HRMS | High Resolution Mass Spectroscopy (electrospray ionisation positive scan) |
| Hünig's base | N-ethyldiisopropylamine |

| | |
|---------------------------------|--|
| Hyflo™ | Hyflo supercel®, from Aldrich Chemical Company |
| KHMDS | potassium bis(trimethylsilyl)amide |
| liq | Liquid |
| LRMS | Low Resolution Mass Spectroscopy (electrospray or thermospray ionisation positive scan) |
| LRMS (ES ⁻) | Low Resolution Mass Spectroscopy (electrospray ionisation negative scan) |
| m | Multiplet |
| m/z | Mass spectrum peak |
| MCI™ gel | High porous polymer, CHP20P 75-150µm, from Mitsubishi Chemical Corporation |
| MeOH | methanol |
| Mukaiyama's reagent | 2-chloro-1-methylpyridinium iodide |
| NaHMDS | sodium bis(trimethylsilyl)amide |
| NMM | N-methylmorpholine |
| NMO | 4-methylmorpholine N-oxide |
| NMP | 1-methyl-2-pyrrolidinone |
| Phenomenex Luna C18 hplc column | Supplied by Phenomenex. Composed of spherical silica particles (size 5 µm or 10 µm) which have a chemically bonded surface of C18 chains. These particles are packed into a stainless steel column of dimensions 2.1cm internal diameter and 25 cm long. |
| psi | Pounds per square inch (1 psi = 6.9 kPa) |
| PyBOP® | Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate |
| PyBrOP® | bromo-tris-pyrrolidino-phosphonium hexafluorophosphate |
| q | Quartet |
| R _f | Retention factor on TLC |
| s | Singlet |
| Sep-Pak® | Reverse phase C ₁₈ silica gel cartridge, Waters Corporation |
| t | Triplet |
| TBDMS-Cl | <i>tert</i> -butyldimethylchlorosilane |
| TFA | trifluoroacetic acid |

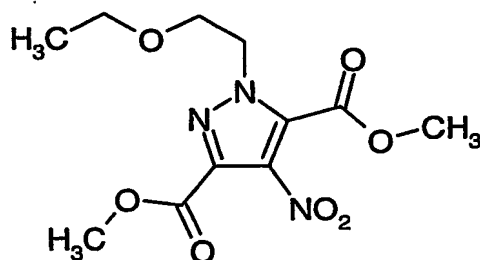
| | |
|----------|---|
| THF | tetrahydrofuran |
| TLC | Thin Layer Chromatography |
| TMS-Cl | chlorotrimethylsilane |
| WSCDI | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| δ | Chemical shift |

The following Examples illustrate the preparation of the compounds of the formula (I):-

5

Preparation 1

Dimethyl 1-(2-ethoxyethyl)-4-nitro-1H-pyrazole-3,5-dicarboxylate

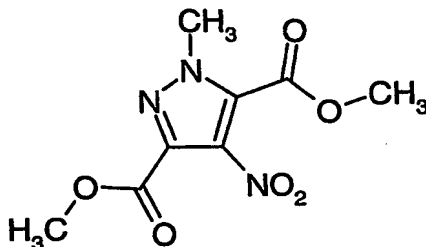


Potassium carbonate (1.32g, 9.57mmol) and 2-ethoxyethyl bromide (1.18mL, 9.57mmol) were added to a solution of dimethyl 4-nitro-1H-pyrazole-3,5-dicarboxylate (EP 1241170, pg. 50, preparation 10) (2g, 9.57mmol) in N,N-dimethylformamide (35mL) and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (200mL) and water (100mL). The organic phase was dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with pentane:ethyl acetate 100:0 to 70:30 in 10% increments to yield the title product, 1.63g.

15

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 1.07 (t, 3H), 3.41 (m, 2H), 3.73 (t, 2H), 3.89 (s, 3H), 3.94 (s, 3H), 4.76 (t, 2H). MS APCI+ m/z 302 $[\text{MH}]^+$

20

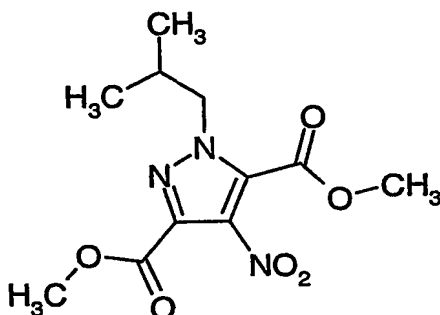
Preparation 2Dimethyl 1-methyl-4-nitro-1H-pyrazole-3,5-dicarboxylate

A solution of dimethyl 4-nitro-1H-pyrazole-3,5-dicarboxylate (EP 1241170, pg. 50, preparation 10) (30g, 0.131mol) in N,N-dimethylformamide (250mL) was treated with caesium carbonate (42.66g, 0.130mol). The reaction mixture was stirred at room temperature for 1 hour and then treated with dimethyl sulphate (12.39mL, 0.130mol). The reaction mixture was stirred at room temperature for 18 hours and was then concentrated *in vacuo*. The residue was partitioned

10 between dichloromethane (550mL) and water (550mL) and the aqueous phase was washed with dichloromethane (2x450mL). The combined organic phases were dried over magnesium sulphate and concentrated *in vacuo* to yield the title product as a white solid, 28.51g.

¹H-NMR (DMSO-D₆, 400MHz) δ : 3.83 (m, 6H), 4.12 (s, 3H). MS APCI+ m/z 244 [MH]⁺

15

Preparation 3Dimethyl 1-isobutyl-4-nitro-1H-pyrazole-3,5-dicarboxylate

20 Dimethyl 4-nitro-1H-pyrazole-3,5-dicarboxylate (EP 1241170, pg. 50, preparation 10) (12.5g, 54.6mmol), 2-methyl-1-propanol (4.95g, 60mmol) and triphenylphosphine (15.72g, 60mmol) were dissolved in tetrahydrofuran (150mL) and the reaction mixture was cooled to 0°C in an ice bath. The reaction mixture

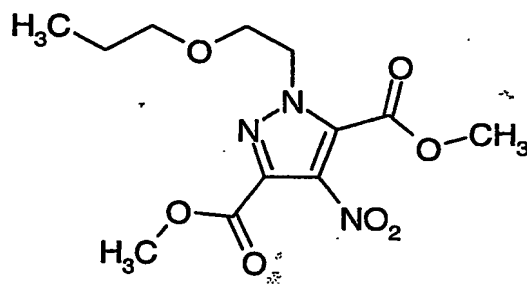
-70°

was treated with diisopropyl azodicarboxylate (12.12g, 60mmol), allowed to return to room temperature and then stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in pentane:ethyl acetate 3:1 (300mL). The solids formed were filtered off and the organic layer separated and adsorbed onto silica. This was purified by column chromatography on silica gel eluting with pentane:ethyl acetate 9:1 to yield the title product.

¹H-NMR (CDCl₃, 400MHz) δ: 0.93 (d, 6H), 2.26 (m, 1H), 3.93 (2xs, 6H), 4.41 (m, 2H). MS APCI+ m/z 286 [MH]⁺

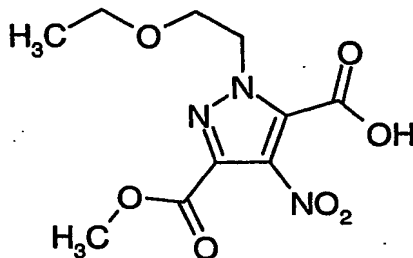
Preparation 4

Dimethyl 4-nitro-1-(2-propoxyethyl)-1H-pyrazole-3,5-dicarboxylate



Dimethyl 4-nitro-1H-pyrazole-3,5-dicarboxylate (EP 1241170, pg. 50, preparation 10) (15g, 60mmol), 2-propoxyethanol (8.2mL, 70mmol) and triphenylphosphine (18.9g, 70mmol) were dissolved in tetrahydrofuran (150mL) and the reaction mixture cooled to 0°C. The reaction mixture was treated with diisopropyl azodicarboxylate (14.2mL, 70mmol) and the reaction mixture stirred at 0°C for 3 hours before being allowed to warm to room temperature. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with ethyl acetate:pentane 15:85 to yield the title product.

¹H-NMR (CD₃OD, 400MHz) δ: 0.82 (t, 3H), 1.47 (m, 2H), 3.34 (t, 2H), 3.78 (t, 2H), 3.91 (m, 6H), 4.76 (t, 2H). MS APCI+ m/z 316 [MH]⁺

Preparation 51-(2-Ethoxyethyl)-4-nitro-1H-pyrazole-3,5-dicarboxylic acid 3-methyl ester

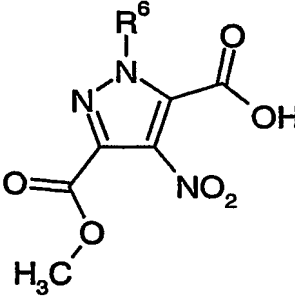
The di-ester of preparation 1 (1.63g, 5.4mmol) was added to a solution of
 5 potassium hydroxide (300mg, 5.9mmol) in methanol (20mL) and the reaction
 mixture stirred at room temperature for 18 hours. The reaction mixture was
 concentrated *in vacuo* and the residue dissolved in water (100mL) and washed
 with ether. The aqueous phase was acidified with 2M hydrochloric acid and
 extracted with dichloromethane (3x100mL). The organic phases were combined,
 10 dried over magnesium sulphate and concentrated *in vacuo* to yield the title
 product, 1.34g.

$^1\text{H-NMR}$ (CD_3OD , 400MHz) δ : 1.07 (t, 3H), 3.47 (m, 2H), 3.80 (t, 2H), 3.88 (s, 3H), 4.77 (t, 2H). MS APCI+ m/z 288 $[\text{MH}]^+$

15

Preparations 6-8

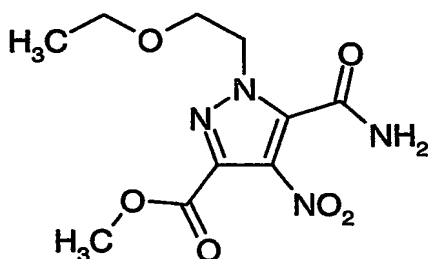
The following compounds were prepared by a method similar to that described for preparation 5 using the appropriate di-ester.

|  | | |
|---|--|--|
| No. | R^6 | Data |
| 6 | $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ | $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 0.92 (d, 6H), 2.27 (m, 1H), 3.99 (s, 3H), 4.42 (m, 2H). MS APCI+ m/z 272 $[\text{MH}]^+$ |

| | | |
|---|---|--|
| 7 | -CH ₃ | ¹ H-NMR (CDCl ₃ , 400MHz) δ: 3.91 (s, 3H), 4.22 (s, 3H), 8.10 (m, 1H). MS APCI+ m/z 230 [MH] ⁺ |
| 8 | -(CH ₂) ₂ O(CH ₂) ₂ CH ₃ | ¹ H-NMR (CD ₃ OD, 400MHz) δ: 0.83 (t, 3H), 1.49 (m, 2H), 3.36 (t, 2H), 3.80 (t, 2H), 3.90 (s, 3H), 4.78 (t, 2H). MS APCI+ m/z 302, [MH] ⁺ , |

Preparation 9

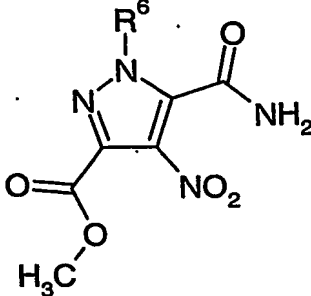
Methyl 5-carbamoyl-1-(2-ethoxyethyl)-4-nitro-1H-pyrazole-3-carboxylate



- 5 Oxalyl chloride (15.7mL, 190mmol) was added steadily to a solution of the carboxylic acid of preparation 5 (17.1g, 59.5mmol) in dichloromethane (300mL). N,N-dimethylformamide (46μL, 6mmol) was then added and the reaction mixture stirred for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue azeotroped from dichloromethane (3x200mL). The product was
- 10 dissolved in tetrahydrofuran (300mL), cooled in ice, treated with 0.88 ammonia (200mL) and stirred for 18 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the residue partitioned between water (200mL) and ethyl acetate. The organics were dried over magnesium sulphate and concentrated *in vacuo* to yield the crude product which triturated in ether to yield
- 15 the title product, 8.2g.
¹H-NMR (DMSO-D₆, 400MHz) δ: 1.03 (t, 3H), 3.38 (m, 2H), 3.70 (t, 2H), 3.86 (s, 3H), 4.36 (t, 2H), 8.30 (m, 1H), 8.46 (m, 1H). MS APCI+ m/z 287 [MH]⁺

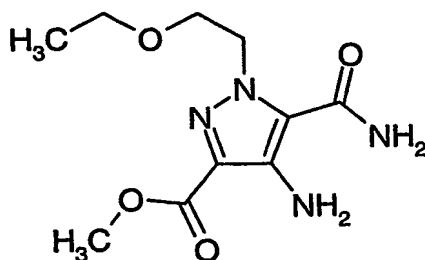
Preparations 10-12

- 20 The following compounds were prepared by a method similar to that described for preparation 9 using the appropriate carboxylic acid.

|  | | |
|---|---|---|
| No. | R ⁶ | Data |
| 10 | -CH ₂ CH(CH ₃) ₂ | ¹ H-NMR (CDCl ₃ , 400MHz) δ: 0.91 (d, 6H), 2.27 (m, 1H), 3.98 (s, 3H), 4.36 (m, 2H), 7.23 (m, 2H). MS APCI+ m/z 271 [MH] ⁺ |
| 11 | -CH ₃ | ¹ H-NMR (DMSO-D ₆ , 400MHz) δ: 3.84 (s, 3H), 3.86 (s, 3H), 8.38 (m, 1H), 8.50 (m, 1H). MS APCI+ m/z 229 [MH] ⁺ |
| 12 | -(CH ₂) ₂ O(CH ₂) ₂ CH ₃ | ¹ H-NMR (DMSO-D ₆ , 400MHz) δ: 0.81 (t, 3H), 1.45 (m, 2H), 3.32 (t, 2H), 3.74 (t, 2H), 3.90 (s, 3H), 4.40 (t, 2H), 8.33 (s, 1H), 8.48 (s, 1H). MS APCI+ m/z 301 [MH] ⁺ |

Preparation 13

Methyl 4-amino-5-carbamoyl-1-(2-ethoxyethyl)-1H-pyrazole-3-carboxylate

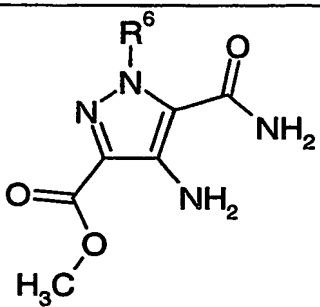


- 5 Palladium(II) hydroxide on carbon (1g) was added to a solution of the nitro compound of preparation 9 (8.2g, 28.6mmol) in methanol (300mL). Ammonium formate (8.8g, 0.14mol) was added portionwise to the reaction mixture over 20 minutes and the reaction mixture then stirred at reflux for 2 hours. The reaction mixture was cooled to room temperature and filtered to remove catalyst. The
- 10 filtrate was concentrated *in vacuo* and azeotroped with toluene to yield the title product, 7.3g.

$^1\text{H-NMR}$ (DMSO-D_6 , 400MHz) δ : 1.04 (t, 3H), 3.32 (m, 2H), 3.66 (t, 2H), 3.78 (s, 3H), 4.49 (t, 2H), 5.12 (m, 2H), 7.50 (m, 2H). MS APCI+ m/z 257 $[\text{MH}]^+$

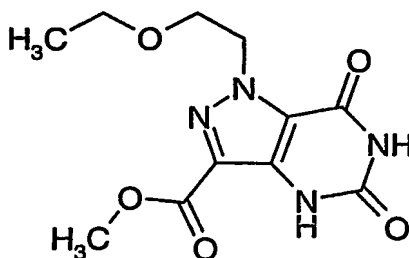
Preparations 14-16

- 5 The following compounds were prepared by a method similar to that described for preparation 13 using the appropriate ester.

|  | | |
|--|--|--|
| No. | R^6 | Data |
| 14 | $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ | $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 0.87 (d, 6H), 2.22 (m, 1H), 3.97 (s, 3H), 4.40 (m, 2H), 4.44 (m, 2H), 6.02 (m, 2H). MS APCI+ m/z 241 $[\text{MH}]^+$ |
| 15 | $-\text{CH}_3$ | $^1\text{H-NMR}$ (DMSO-D_6 , 400MHz) δ : 3.69 (s, 3H), 3.92 (s, 3H), 5.17 (m, 2H), 7.37 (brm, 2H). MS APCI+ m/z 199 $[\text{MH}]^+$ |
| 16 | $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CH}_3$ | $^1\text{H-NMR}$ (CD_3OD , 400MHz) δ : 0.84 (t, 3H), 1.51 (m, 2H), 3.40 (t, 2H), 3.83 (t, 2H), 3.89 (s, 3H), 4.56 (t, 2H). MS APCI+ m/z 271, $[\text{MH}]^+$, |

Preparation 17

Methyl 1-(2-ethoxyethyl)-5,7-dioxo-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-d]pyrimidine-3-carboxylate

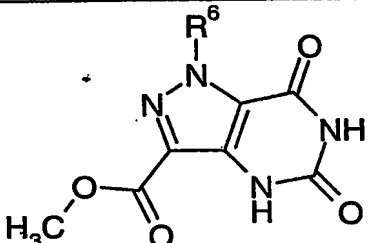


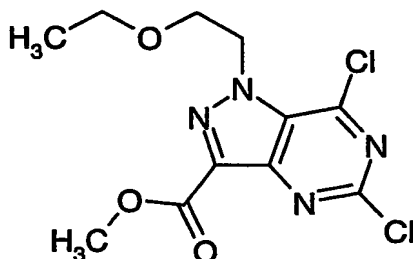
N,N'-Carbonyldiimidazole (5.54g, 34.2mmol) was added to a solution of the amide of preparation 13 (7.3g, 28.5mol) in N,N-dimethylformamide (250mL) and the reaction mixture stirred at room temperature for 1 hour and then at 90°C for 18 hours. The reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The residue was sonicated in acetone (200mL) and concentrated *in vacuo* to yield the title product, 5.3g.

¹H-NMR (DMSO-D₆, 400MHz) δ: 0.99 (t, 3H), 3.37 (m, 2H), 3.77 (t, 2H), 3.82 (s, 3H), 4.64 (t, 2H). MS ES- m/z 281 [M-H]⁻

Preparations 18-20

The following compounds were prepared by a method similar to that described for preparation 17 using the appropriate ester.

|  | | |
|---|---|---|
| No. | R ⁶ | Data |
| 18 | -CH ₂ CH(CH ₃) ₂ | ¹ H-NMR (DMSO-D ₆ , 400MHz) δ: 0.82 (d, 6H), 2.16 (m, 1H), 3.83 (s, 3H), 4.32 (m, 2H), 10.75 (m, 1H), 11.34 (m, 1H). MS APCI+ m/z 267 [MH] ⁺ |
| 19 | -CH ₃ | ¹ H-NMR (DMSO-D ₆ , 400MHz) δ: 3.80 (s, 3H), 4.08 (s, 3H). MS APCI- m/z 223 [M-H] ⁻ |
| 20 | -(CH ₂) ₂ O(CH ₂) ₂ CH ₃ | ¹ H-NMR (DMSO-D ₆ , 400MHz) δ: 0.72 (t, 3H), 1.37 (m, 2H), 3.28 (t, 2H), 3.76 (t, 2H), 3.82 (s, 3H), 4.64 (t, 2H), 10.77 (s, 1H), 11.37 (s, 1H). MS APCI+ m/z 295, [M-H] ⁻ |

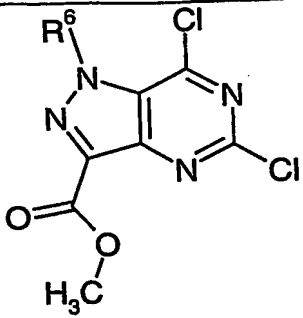
Preparation 21Methyl 5,7-dichloro-1-(2-ethoxyethyl)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxylate

Phosphorous oxychloride (6.5mL, 70mmol) and tetraethylammonium chloride
5 (3.47g, 21mmol) were added to a solution of the dione of preparation 17 (1.97g, 7mmol) in propionitrile (28mL) and the reaction mixture refluxed for 4 hours. Additional phosphorous oxychloride (2.5mL) was added and the reaction mixture was then stirred at reflux for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue re-dissolved in propionitrile (50mL) and phosphorous
10 oxychloride (6.5mL) and stirred at reflux for a further 18 hours. The reaction mixture was then concentrated *in vacuo* and the residue partitioned between dichloromethane (300mL) and water (50mL). The organics were dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with ethyl acetate:pentane 0:100 to
15 25:75 to yield the title product, 1.98g.

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 1.03 (t, 3H), 3.40 (m, 2H), 3.87 (t, 2H), 4.06 (s, 3H), 4.98 (t, 2H). MS APCI+ m/z 319 $[\text{MH}]^+$

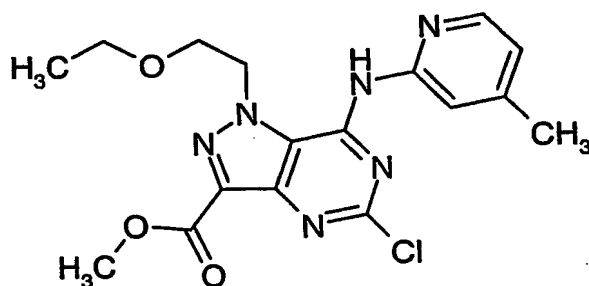
Preparations 22-24

20 The following compounds were prepared by a method similar to that described for preparation 21 using the appropriate ester.

|  | | |
|---|---|--|
| No. | R ⁶ | Data |
| 22 | -CH ₂ CH(CH ₃) ₂ | ¹ H-NMR (CDCl ₃ , 400MHz) δ: 0.95 (d, 6H), 2.38 (m, 1H), 4.08 (s, 3H), 4.61 (m, 2H). MS APCI+ m/z 303 [MH] ⁺ |
| 23 | -CH ₃ | ¹ H-NMR (CDCl ₃ , 400MHz) δ: 4.05 (s, 3H), 4.49 (s, 3H). MS APCI+ m/z 261 [MH] ⁺ |
| 24 | -(CH ₂) ₂ O(CH ₂) ₂ CH ₃ | ¹ H-NMR (DMSO-D ₆ , 400MHz) δ: 0.65 (t, 3H), 1.33 (m, 2H), 3.26 (t, 2H), 3.82 (t, 2H), 3.93 (s, 3H), 4.94 (t, 2H). MS APCI+ m/z 333, [MH] ⁺ |

Preparation 25

Methyl 5-chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxylate



5

2-Amino-4-methylpyridine (1.34g, 12.4mmol) was added to a solution of the dichloro compound of preparation 21 (1.98, 6.2mmol) in dimethyl sulfoxide (10mL) and the reaction mixture stirred at 35°C for 5 hours. The reaction mixture was partitioned between dichloromethane (300mL) and water (500mL) and the organics washed with water (3x100mL), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica, eluting with dichloromethane:acetonitrile 98:2.

10

-78-

Appropriate fractions were concentrated *in vacuo*, triturated with ether (50mL), filtered and the solid dried to yield the title product, 1.2g.

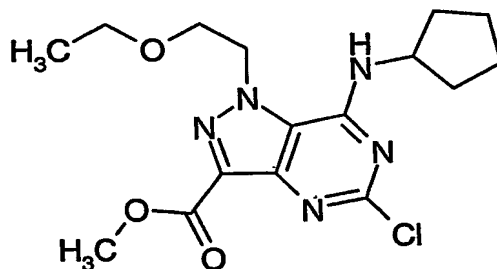
$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 1.06 (t, 3H), 2.49 (s, 3H), 3.62 (m, 2H), 4.00 (t, 2H), 4.06 (s, 3H), 5.05 (m, 2H), 6.98 (m, 1H), 8.16 (m, 1H), 8.50 (m, 1H). MS APCI+ m/z 391 $[\text{MH}]^+$

Preparations 26-31

The following compounds were prepared by a method similar to that described for preparation 25 using the appropriate HNR^1R^2 amine and chloro compound.

| No. | R^6 | R^{7A} | R^{7B} | Data |
|-----|--|-----------------|-----------------|--|
| 26 | $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ | H | $-\text{CH}_3$ | $^1\text{H-NMR}$ (DMSO-D_6 , 400MHz) δ : 0.84 (d, 6H), 2.22 (m, 1H), 2.39 (s, 3H), 3.86 (s, 3H), 4.67 (m, 2H), 6.92 (m, 1H), 7.60 (m, 1H), 8.08 (m, 1H). MS APCI+ m/z 375 $[\text{MH}]^+$ |
| 27 | $-\text{CH}_3$ | H | $-\text{CH}_3$ | $^1\text{H-NMR}$ (DMSO-D_6 , 400MHz) δ : 2.40 (s, 3H), 3.84 (s, 3H), 4.40 (s, 3H), 6.95 (m, 1H), 7.68 (m, 1H), 8.15 (m, 1H). MS APCI+ m/z 333 $[\text{MH}]^+$ |
| 28 | $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{CH}_3$ | H | $-\text{CH}_3$ | $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 0.80(t, 3H), 1.45(m, 2H), 2.55(s, 3H), 3.45(t, 2H), 3.85(t, 2H), 4.05(s, 3H), 4.86(t, 2H), 7.05(m, 1H), 8.16(m, 1H), 8.49(m, 1H). MS APCI+ m/z 405 $[\text{MH}]^+$ |

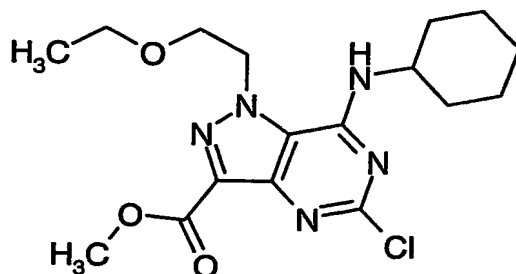
| | | | | |
|----|---|----------------|---|--|
| 29 | $-(\text{CH}_2)_2\text{OCH}_2\text{CH}_3$ | $-\text{CH}_3$ | H | $^1\text{H-NMR}$ (DMSO-D_6 , 400MHz) δ : 1.01 (t, 3H), 2.26 (s, 3H), 3.52 (m, 2H), 3.88 (m, 5H), 4.96 (m, 2H), 7.76 (m, 1H), 8.03 (m, 1H), 8.20 (m, 1H). MS APCI+ m/z 391 $[\text{MH}]^+$ |
| 30 | $-(\text{CH}_2)_2\text{OCH}_2\text{CH}_3$ | H | H | $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 1.15 (t, 3H), 3.63 (m, 2H), 4.01 (t, 2H), 4.08 (s, 3H), 4.97 (m, 2H), 7.17 (t, 2H), 7.86 (t, 1H), 8.36 (m, 1H), 8.56 (m, 1H). MS APCI+ m/z 377 $[\text{MH}]^+$ |

Preparation 31Methyl 5-chloro-7-(cyclopentylamino)-1-(2-ethoxyethyl)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxylate

- 5 Cyclopentylamine (4.64mL, 47mmol) was added dropwise to an ice-cooled solution of the dichloro compound of preparation 21 (3.0g, 9.4mmol) in dimethylsulphoxide (8mL). Once addition was complete, the reaction was stirred for a further 10 minutes at room temperature. The reaction mixture was diluted
- 10 with dichloromethane, and the mixture washed with water (x2). The solution was dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using an elution gradient of ethyl acetate:pentane (25:75 to 50:50) to give the title compound as a white solid, 2.3g.

¹H-NMR (CDCl₃, 400MHz) δ: 1.17 (t, 3H), 1.50 (m, 2H), 1.73 (m, 4H), 2.21 (m, 2H), 3.56 (q, 2H), 3.93 (t, 2H), 4.04 (s, 3H), 4.50 (m, 1H), 4.70 (t, 2H), 7.35 (br, d, 1H). MS ES+ m/z 382 [MH]⁺.

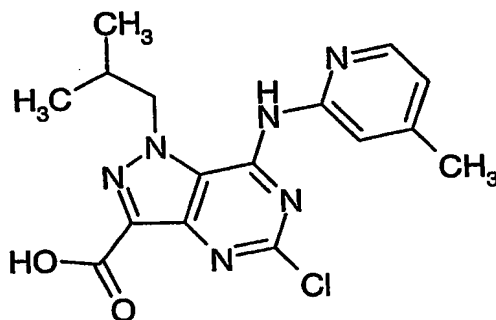
5

Preparation 32Methyl 5-chloro-7-(cyclohexylamino)-1-(2-ethoxyethyl)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxylate

10 The dichloro compound of preparation 21 (2.50g, 7.84mmol) was dissolved in tetrahydrofuran (10mL) and the solution treated dropwise with a solution of cyclohexylamine (4.48mL, 39.20mmol) in tetrahydrofuran (10mL) whilst being cooled in an ice bath. The reaction mixture was stirred for 15 minutes at room temperature. The reaction mixture was diluted with water (50mL) and ethyl acetate (50mL) and stirred for 1 hour. The ethyl acetate layer was separated, washed with water, dried over magnesium sulphate and concentrated *in vacuo*.
15 The residue was triturated with ether to yield 2.25g of the desired product.

¹H-NMR (CDCl₃, 400MHz) δ: 1.18 (t, 3H), 1.27 (m, 2H), 1.47 (m, 2H), 1.53-1.75 (m, 2H), 1.78 (m, 2H), 2.12 (m, 2H), 3.76 (m, 2H), 3.92 (t, 2H), 4.00 (s, 3H), 4.12 (m, 1H), 4.70 (t, 2H), 7.20 (d, 1H). MS ES+ m/z 382 [MH]⁺

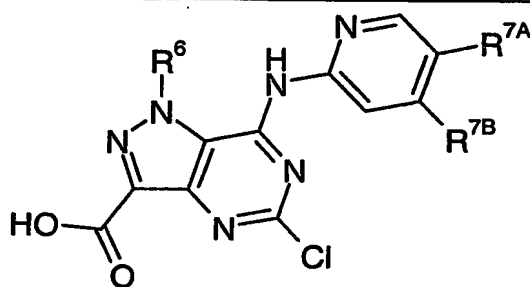
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Preparation 335-Chloro-1-isobutyl-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxylic acid

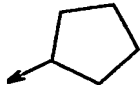
- 5 The ester of preparation 26 (1.00g, 2.67mmol) and 1M aqueous sodium hydroxide solution (5.34mL, 5.34mmol) were dissolved in dioxane (25mL) and the reaction mixture stirred under nitrogen for 4 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the residue dissolved in water (10mL) and acidified with 1M citric acid solution. The precipitate formed was
- 10 filtered off and dried in an oven at 55°C for 18 hours to yield the title product. ¹H-NMR (DMSO-D₆, 400MHz) δ: 0.83 (d, 6H), 2.21 (m, 1H), 2.41 (s, 3H), 4.65 (m, 2H), 6.93 (m, 1H), 7.60 (m, 1H), 8.08 (m, 1H). MS APCI+ m/z 361 [MH]⁺

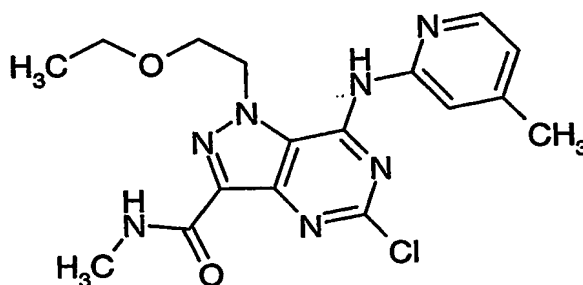
Preparations 34-38

- 15 The following compounds were prepared by a method similar to that described for preparation 33 using the appropriate ester.



| No. | R ⁶ | R ^{7A} | R ^{7B} | Data |
|-----|---|---|------------------|---|
| 34 | -(CH ₂) ₂ OCH ₂ CH ₃ | H | -CH ₃ | ¹ H-NMR (DMSO-D ₆ , 400MHz) δ: 1.00 (t, 3H), 2.37 (s, 3H), 3.47 (m, 2H), 3.84 (m, 2H), 4.91 (m, 2H), 6.94 (m, 1H), 7.82 (m, 1H), 8.17 (m, 1H). MS APCI+ m/z 377 [MH] ⁺ |
| 35 | -CH ₃ | H | -CH ₃ | ¹ H-NMR (DMSO-D ₆ , 400MHz) δ: 2.37 (s, 3H), 4.35 (s, 3H), 6.93 (m, 1H), 7.68 (m, 1H), 8.12 (d, 1H). MS ES- m/z 317 [M-H] ⁻ |
| 36 | -(CH ₂) ₂ OCH ₂ CH ₃ | -CH ₃ | H | ¹ H-NMR (DMSO-D ₆ , 400MHz) δ: 1.03 (t, 3H), 2.30 (s, 3H), 3.56 (m, 2H), 3.86 (m, 2H), 4.88 (m, 2H), 7.77 (m, 1H), 8.08 (m, 1H), 8.17 (m, 1H). MS ES- m/z 375 [M-H] ⁻ |
| | | | | |
| No. | R ¹ | Data | | |
| 37 | | ¹ H-NMR (CDCl ₃ , 400MHz) δ: 1.00 (t, 3H), 1.18 (m, 1H), 1.38 (m, 4H), 1.62 (m, 1H), 1.74 (m, 2H), 1.96 (m, 2H), 3.40 (t, 2H), 3.72 (m, 2H), 4.03 (m, 1H), 4.73 (m, 2H), 7.26(d, 1H). MS ES- m/z 352 [M-H] ⁻ | | |

| | | |
|----|---|---|
| 38 |  | $^1\text{H-NMR}$ (DMSO- D_6 , 400MHz) δ : 0.99(t, 3H), 1.59(m, 4H), 1.72(m, 2H), 2.03(m, 2H), 3.40(q, 2H), 3.74(t, 2H), 4.41(m, 1H), 4.74(t, 2H), 7.35(d, 1H) |
|----|---|---|

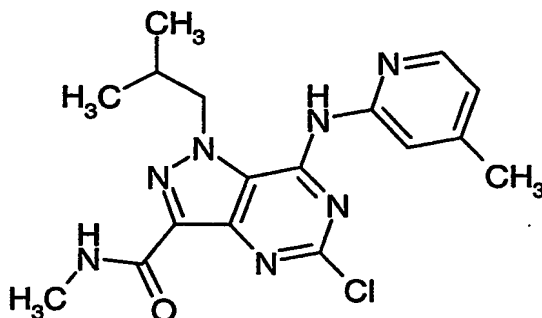
Preparation 395-Chloro-1-(2-ethoxyethyl)-N-methyl-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

5

The carboxylic acid of preparation 34 (753mg, 2.0mmol) was added to a solution of 1-hydroxybenzotriazole hydrate (297mg, 2.20mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (421mg, 2.2mmol) and N-ethyldiisopropylamine (383 μL , 2.2mmol) in N,N-dimethylformamide (10mL) and the mixture stirred for 10 minutes at room temperature. An 8M solution of methylamine in ethanol (380 μL , 3.0mmol) was added and the reaction mixture stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue taken up in dichloromethane (100mL), washed with water (100mL), sodium hydrogencarbonate solution (50mL) and 1M citric acid solution (50mL), dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 97:3 to yield the title product, 450mg.

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 1.18 (t, 3H), 2.39 (s, 3H), 3.00 (s, 3H), 3.62 (m, 2H), 3.96 (t, 2H), 4.77 (t, 2H), 4.99 (m, 1H), 6.83 (d, 1H), 8.17 (d, 1H), 8.24 (s, 1H). MS APCI+ m/z 390 $[\text{MH}]^+$

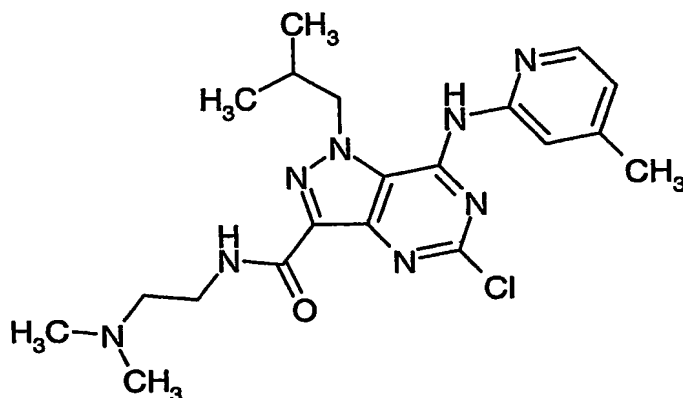
20

Preparation 405-Chloro-1-isobutyl-N-methyl-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

- 5 A solution of the carboxylic acid of preparation 33 (360mg, 1.0mmol) in N,N-dimethylformamide (5mL) was treated with 1-hydroxybenzotriazole hydrate (149mg, 1.10mmol), N-ethyl-diisopropylamine (260μL, 1.5mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (215mg, 1.10mmol) and the reaction mixture stirred for 20 minutes at room temperature. An 8M solution
- 10 of methylamine in ethanol (38μL, 1.10mmol) was added and the reaction mixture stirred at room temperature for 48 hours. The reaction mixture was concentrated *in vacuo*, partitioned between ethyl acetate (50mL) and water (50mL) and the organics separated and washed with water (2x50mL). The organic layer was dried over magnesium sulphate and concentrated *in vacuo* and the residue was
- 15 purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 98:2 to yield the title product as a yellow solid, 360mg.

¹H-NMR (CDCl₃, 400MHz) δ: Rotamers 0.91 (2xd, 6H), 2.38+2.47 (2xs, 3H), 2.43 (m, 1H), 2.97+3.11 (2xd, 3H), 4.71+4.76 (2xm, 2H), 7.42-7.65 (m, 3H). MS

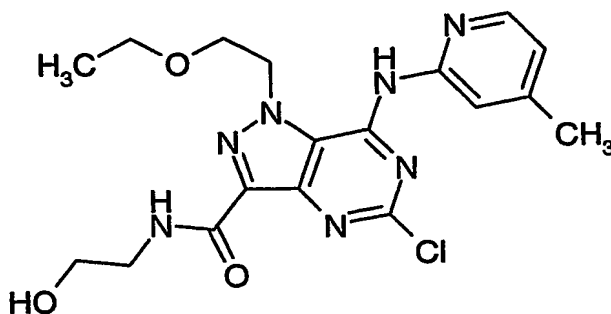
20 APCI+ m/z 374 [MH]⁺

Preparation 415-Chloro-N-(2-(dimethylamino)ethyl)-1-isobutyl-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

- 5 The title compound was prepared by a method similar to that described for preparation 40 using N,N-dimethylethylenediamine and the acid of preparation 33 to yield the product as a yellow solid in 88% yield.

¹H-NMR (CDCl₃, 400MHz) δ: 0.90 (d, 6H), 2.36-2.44 (m, 9H), 2.55 (m, 1H), 2.66 (m, 2H), 3.71 (m, 2H), 4.71 (m, 2H), 6.65 (m, 1H), 7.73 (m, 1H), 8.35 (m, 1H).

- 10 MS APCI+ m/z 431 [MH]⁺

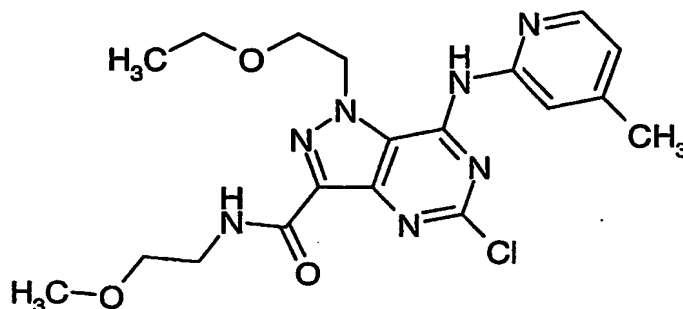
Preparation 425-Chloro-1-(2-ethoxyethyl)-N-(2-hydroxyethyl)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

15

The title compound was prepared by a method similar to that described for preparation 40 using 2-aminoethanol and the acid of preparation 34.

¹H-NMR (CD₃OD, 400MHz) δ: 1.10 (m, 3H), 2.41 (s, 3H), 3.51-3.64 (m, 4H), 3.77 (m, 2H), 3.96 (m, 2H), 4.90 (m, 2H), 6.96 (m, 1H), 7.56 (m, 1H), 8.12 (m, 1H).

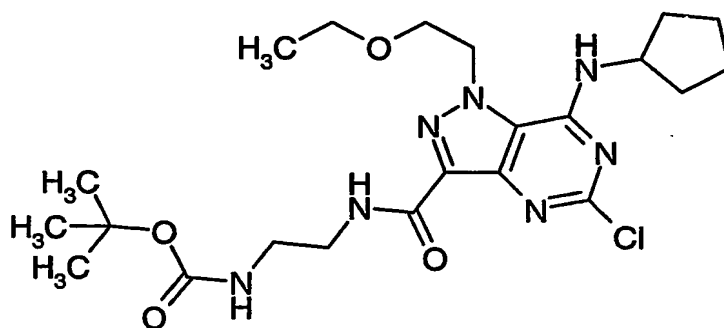
- 20 MS APCI+ m/z 420 [MH]⁺

Preparation 435-Chloro-1-(2-ethoxyethyl)-N-(2-methoxyethyl)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

- 5 The title compound was prepared by a method similar to that described for preparation 40 using 2-methoxyethylamine and the acid of preparation 34.

¹H-NMR (CDCl₃, 400MHz) δ: 1.07 (t, 3H), 2.46 (s, 3H), 3.43 (s, 3H), 3.62 (m, 4H), 3.84 (m, 2H), 3.99 (m, 2H), 4.95 (m, 2H), 6.97 (m, 1H), 7.23 (m, 1H), 8.18 (m, 1H),

10

Preparation 44*tert*-Butyl (2-([5-chloro-7-(cyclopentylamino)-1-(2-ethoxyethyl)-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl]amino)ethyl)carbamate

- 15 The acid of preparation 38 (353.8mg, 0.80mmol) was suspended in N,N-dimethylformamide (6mL) and the solution treated with N,N'-carbonyldiimidazole (208mg, 1.28mmol) and stirred at room temperature for 1 hour. The solution was treated with (2-amino-ethyl)-carbamic acid *tert*-butyl ester (160.2mg, 1.28mmol) and the reaction mixture stirred at room temperature for 5 hours. The reaction
- 20 mixture was concentrated *in vacuo* and the residue dissolved in dichloromethane and washed with water (x2) and brine. The solution was dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column

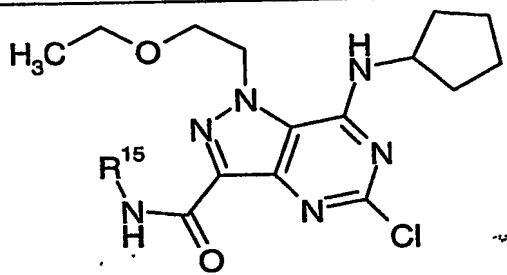
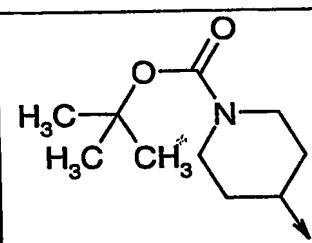
chromatography on silica gel eluting with ethyl acetate to yield the title product as a colourless oil.

$^1\text{H-NMR}$ (CD_3OD , 400MHz) δ : 1.12 (t, 3H), 1.39 (s, 9H), 1.62 (m, 2H), 1.72 (m, 2H), 1.82 (m, 2H), 2.19 (m, 2H), 3.31 (m, 2H), 3.55 (m, 4H), 3.89 (t, 2H), 4.50 (m, 1H), 4.76 (t, 2H)

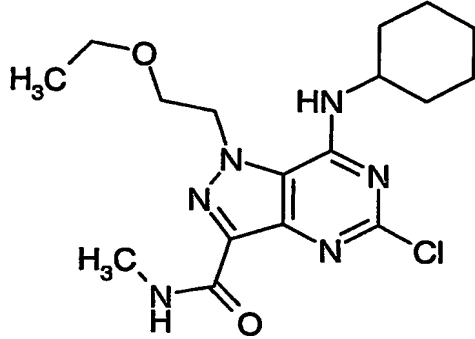
5

Preparations 45-49

The following compounds were prepared by a method similar to that described for preparation 44 using the appropriate acid and $\text{NHR}^{15}\text{R}^{16}$ amine.

|  | | |
|--|---|---|
| No. | R^{15} | Data |
| 45 |  | $^1\text{H-NMR}$ (CD_3OD , 400MHz) δ : 1.12 (t, 3H), 1.48 (s, 9H), 1.52-1.73 (m, 6H), 1.82 (m, 2H), 2.01 (m, 2H), 2.18 (m, 2H), 3.11 (t, 2H), 3.54 (m, 2H), 3.89 (t, 2H), 3.98 (m, 2H), 4.17 (m, 1H), 4.50 (m, 1H), 4.76 (t, 2H) |
| 46 | $-(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$ | $^1\text{H-NMR}$ (CD_3OD , 400MHz) δ : 1.12 (t, 3H), 1.63 (m, 2H), 1.71 (m, 2H), 1.82 (m, 2H), 2.19 (m, 2H), 2.33 (s, 6H), 2.62 (t, 2H), 3.54 (m, 2H), 3.62 (t, 2H), 3.89 (t, 2H), 4.50 (m, 1H), 4.75 (t, 2H) |
| 47 | $-(\text{CH}_2)_2\text{OCH}_3$ | $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 1.12 (t, 3H), 1.62 (m, 2H), 1.70 (m, 2H), 1.80 (m, 2H), 2.18 (m, 2H), 3.40 (s, 3H), 3.55 (m, 2H), 3.60 (m, 2H), 3.64 (t, 2H), 3.88 (m, 2H), 4.48 (m, 1H), 4.75 (m, 2H), 7.98 (s, 1H), 8.60 (m, 1H). MS ES+ m/z 433 $[\text{MNa}]^+$ |

| | | |
|----|------------------|--|
| 48 | -CH ₃ | ¹ H-NMR (CDCl ₃ , 400MHz) δ: 1.12 (t, 3H), 1.63 (m, 2H), 1.71 (m, 2H), 1.82 (m, 2H), 2.20 (m, 2H), 3.00 (s, 3H), 3.53 (m, 2H), 3.88 (t, 2H), 4.50 (m, 1H), 4.73 (t, 2H), 7.48 (d, 1H). MS ES+ m/z 389 [MNa] ⁺ |
|----|------------------|--|

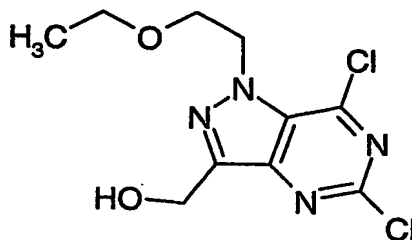
| No. | | Data |
|-----|---|--|
| 49 |  | ¹ H-NMR (CDCl ₃ , 400MHz) δ: 1.17 (t, 3H), 1.20-1.35 (m, 3H), 1.41-1.55 (m, 2H), 1.65-1.84 (m, 3H), 2.11 (m, 2H), 3.10 (d, 3H), 3.56 (m, 2H), 3.92 (t, 2H), 4.16 (m, 1H), 4.68 (t, 2H), 7.24 (m, 1H), 8.14 (m, 1H). MS ES+ m/z 381 [MH] ⁺ |

- Preparations 47 and 48 were not purified by column chromatography
- Preparations 48 and 49 used an 8M solution of methylamine in ethanol to provide the HNR¹⁵R¹⁶ amine.

5

Preparation 50

[5,7-Dichloro-1-(2-ethoxyethyl)-1H-pyrazolo[4,3-d]pyrimidin-3-yl]methanol



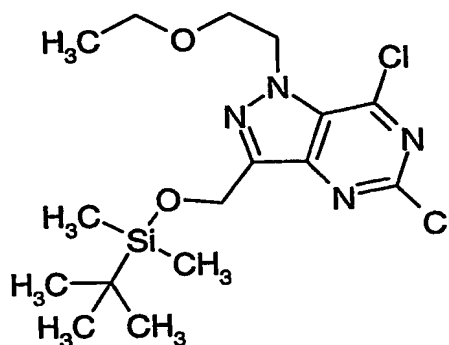
- 10 The dichloro compound of preparation 21 (2.4g, 7.52mmol) was dissolved in tetrahydrofuran (60mL) and the reaction mixture cooled to -78°C. DIBAL (37.6mL, 37.6mmol) in tetrahydrofuran (20mL) was added dropwise over 10 minutes and the reaction mixture stirred at -78°C for 10 minutes and then at -10°C for 1 hour. The reaction mixture was cooled to -78°C, quenched with ammonium chloride solution (25mL) and allowed to return to room temperature. The reaction mixture was diluted with dichloromethane (200mL) and water (100mL) and the
- 15

solution filtered through ArBOCel®, washing through with dichloromethane (3x100mL). The organic phase was separated, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol 99:1 to yield the title product, 1.67g.

¹H-NMR (CDCl₃, 400MHz) δ: 1.08 (t, 3H), 3.42 (m, 2H), 3.80 (m, 2H), 4.90 (m, 2H), 5.10 (s, 2H). MS APCI+ m/z 291 [MH]⁺

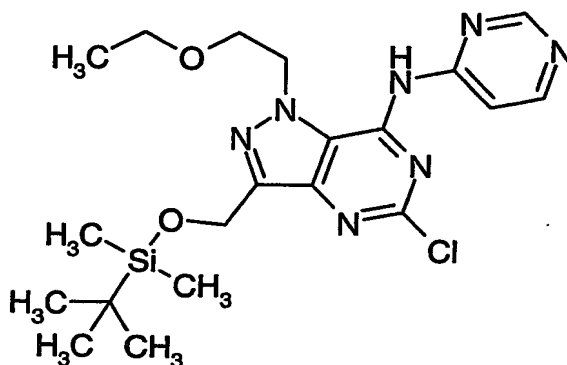
Preparation 51

3-(*tert*-Butyldimethylsilyloxymethyl)-5,7-dichloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine



The alcohol of preparation 50 (1.32g, 4.53mmol) was dissolved in dichloromethane (25mL) and the solution treated with imidazole (339mg, 4.98mmol) and then *tert*-butyldimethylsilyl chloride (750mg, 4.98mmol). The reaction mixture was then stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (200mL) and washed with 10% potassium carbonate solution (100mL). The organic phase was dried over sodium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol 99:1 to yield the title product, 1.56g.

¹H-NMR (CDCl₃, 400MHz) δ: 0.00 (s, 6H), 0.78 (s, 9H), 0.93 (t, 3H), 3.29 (q, 2H), 3.71 (t, 2H), 4.72 (m, 2H), 4.94 (s, 2H). MS APCI+ m/z 405[MH]⁺

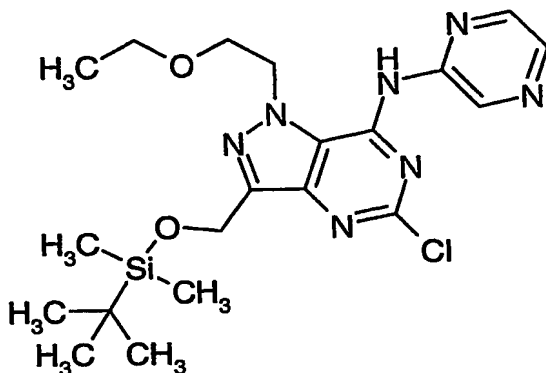
Preparation 52*N*-[3-(*tert*-Butyldimethylsilyloxymethyl)-5-chloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]pyrimidin-4-ylamine

- 5 Pyrimidin-4-ylamine (1.10g, 11.55mmol) was dissolved in tetrahydrofuran (30mL) and the solution treated with sodium hexamethyldisilazide (2.12g, 11.55mmol) and stirred at room temperature for 20 minutes. The reaction mixture was treated with a solution of the dichloro compound of preparation 51 (1.56g, 3.85mmol) in tetrahydrofuran (10mL) and the reaction mixture stirred for 90
- 10 minutes at room temperature. The reaction mixture was quenched with ammonium chloride solution (100mL) and extracted with dichloromethane (200mL). The organic phase was separated, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol 97:3 to yield
- 15 the title product, 830mg.

¹H-NMR (CDCl₃, 400MHz) δ: 0.00 (s, 6H), 0.77 (s, 9H), 1.08 (t, 3H), 3.54 (q, 2H), 3.80(m, 2H), 4.63 (m, 2H), 4.90 (s, 2H), 8.33 (d, 1H), 8.51 (d, 1H), 8.77 (s, 1H).
MS APCI+ m/z 464 [MH]⁺

Preparation 53

N-[3-(*tert*-Butyldimethylsilyloxymethyl)-5-chloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]pyrazin-2-ylamine



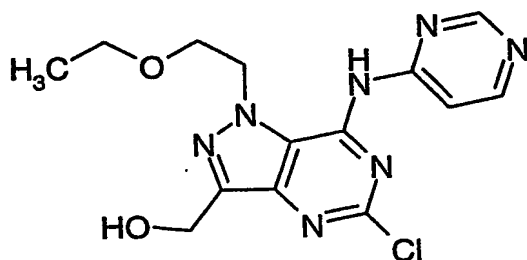
- 5 The title compound was prepared by a method similar to that described for preparation 52 using aminopyrazine.

¹H-NMR (CDCl₃, 400MHz) δ: 0.18 (s, 6H), 0.93 (s, 9H), 1.21 (t, 3H), 3.65 (m, 2H), 3.97 (m, 2H), 4.80 (m, 2H), 5.06 (m, 2H), 8.30 (m, 2H), 9.77 (m, 1H), 10.17 (m, 1H)

10

Preparation 54

[5-Chloro-1-(2-ethoxyethyl)-7-(pyrimidin-4-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]methanol



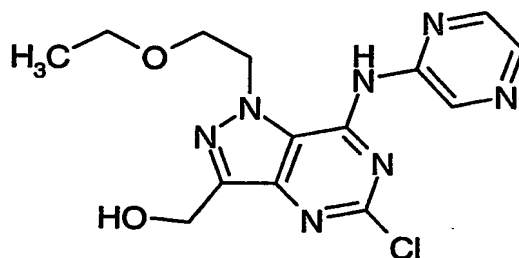
- 15 The protected alcohol of preparation 52 (2.0g, 1.76mmol) was dissolved in tetrahydrofuran (40mL) and the solution treated with a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (8.63mL). The reaction mixture was stirred for 90 minutes at room temperature and was then treated with additional tetrabutylammonium fluoride solution (4.32mL) and stirred for another
- 20 hour. The reaction mixture was diluted with water (50mL) and the aqueous extracted with ethyl acetate (3x50mL). The combined organics were dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified

by column chromatography on silica gel eluting with dichloromethane:methanol 99:1 to 95:5 to yield the title product, 1.25g.

¹H-NMR (CDCl₃, 400MHz) δ: 1.26 (t, 3H), 3.70 (q, 2H), 3.97 (m, 2H), 4.76 (m, 2H), 5.10 (s, 2H), 8.51 (d, 1H), 8.72 (d, 1H), 8.99 (s, 1H). MS APCI+ m/z 350 [MH]⁺

Preparation 55

5-Chloro-1-(2-ethoxyethyl)-7-(pyrazin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidin-3-yl]methanol

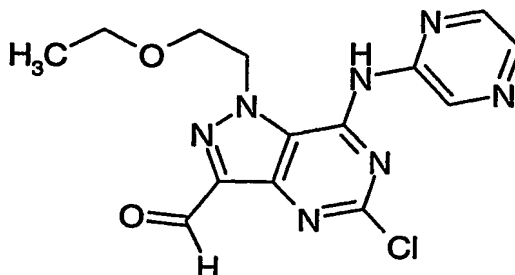


The title compound was prepared by a method similar to that described for preparation 54 using the protected alcohol of preparation 53.

¹H-NMR (CDCl₃, 400MHz) δ: 1.22 (t, 3H), 3.66 (m, 2H), 3.98 (m, 2H), 4.80 (m, 2H), 5.08 (s, 2H), 8.34 (m, 2H), 9.80 (m, 1H), 10.22 (m, 1H)

Preparation 56

5-Chloro-1-(2-ethoxyethyl)-7-(pyrazin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carbaldehyde



The alcohol of preparation 55 (251mg, 0.72mmol) was dissolved in dichloromethane (12mL) and the solution cooled to 0°C in an ice bath. Dess Martin periodinane (456mg, 1.08mmol) was added and the reaction mixture stirred at room temperature for 2 hours. The reaction mixture was treated with a saturated solution of sodium thiosulphate in water (7.8mL) and then with

saturated sodium hydrogencarbonate solution (7.8mL) and ether (7.8mL). The reaction mixture was stirred at room temperature for 15 minutes, the organic phase separated and the aqueous extracted with dichloromethane (x3). The organics were combined, dried over sodium sulphate and concentrated *in vacuo*.

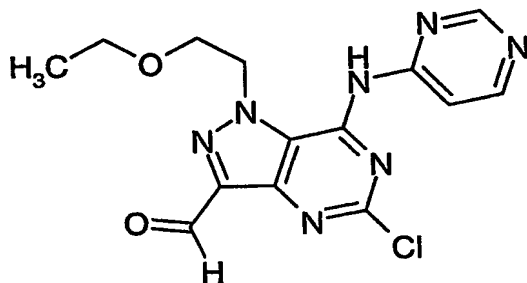
- 5 The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol 99:1 to yield the title product, 200mg.

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 1.22 (t, 3H), 3.69 (m, 2H), 4.06 (m, 2H), 4.92 (m, 2H), 7.22 (m, 1H), 8.32 (m, 1H), 8.40 (m, 1H), 9.77 (m, 1H), 10.35 (m, 1H)

10

Preparation 57

5-Chloro-1-(2-ethoxyethyl)-7-(pyrimidin-4-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carbaldehyde

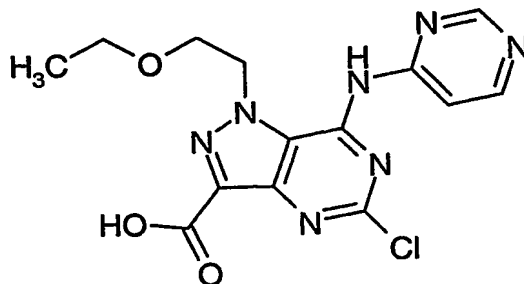


- 15 This compound was prepared by a method similar to that described for preparation 56 using the alcohol of preparation 54.

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 1.23 (t, 3H), 3.72 (m, 2H), 4.06 (t, 2H), 4.93 (m, 2H), 8.36 (m, 1H), 8.40 (m, 1H), 9.77 (m, 1H), 10.37 (m, 1H)

Preparation 58

- 20 5-Chloro-1-(2-ethoxyethyl)-7-(pyrimidin-4-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxylic acid

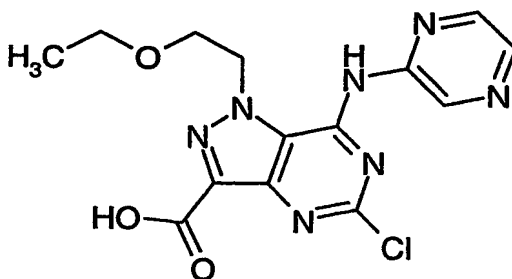


The aldehyde of preparation 57 (220mg, 0.63mmol) was dissolved in *tert*-butanol (40mL) and the solution treated with a 2M solution of 2-methyl-2-butene in tetrahydrofuran (44mL). The solution was stirred at room temperature and then treated dropwise with a solution of sodium chlorite (683mg, 7.59mmol) and sodium dihydrogen orthophosphate (699mg, 5.82mmol) in water (8mL) over 5 minutes. The reaction mixture was stirred at room temperature for 30 minutes. Water (40mL) and dichloromethane (40mL) were added to the reaction mixture and the phases separated. The aqueous layer was extracted with dichloromethane (2x40mL) and the aqueous was then acidified to pH 3 and extracted once more with dichloromethane (2x40mL). These organics were combined, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with first dichloromethane:methanol 97:3 and then dichloromethane:methanol:acetic acid 85:15:1 to yield the title product, 194mg.

¹H-NMR (CD₃OD, 400MHz) δ : 1.20 (t, 3H), 3.68 (m, 2H), 4.01 (t, 2H), 4.92 (t, 2H), 8.42 (m, 1H), 8.68 (m, 1H), 8.87 (m, 1H). MS APCI+ m/z 364 [MH]⁺

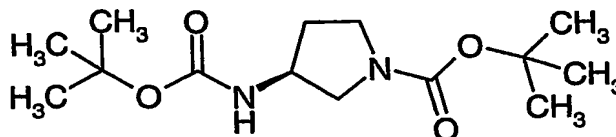
Preparation 59

5-Chloro-1-(2-ethoxyethyl)-7-(pyrazin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylic acid



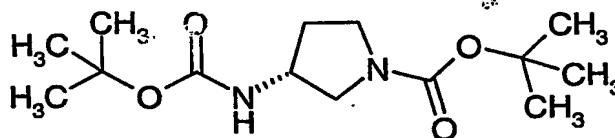
The title compound was prepared by a method similar to that described for preparation 58 using the aldehyde of preparation 56.

¹H-NMR (CD₃OD, 400MHz) δ : 1.20 (m, 3H), 3.65 (m, 2H), 3.99 (m, 2H), 4.96 (m, 2H), 8.36 (m, 1H), 8.42 (m, 1H), 9.60 (m, 1H). MS APCI+ m/z 364 [MH]⁺

Preparation 60*tert*-Butyl (3*S*)-3-(*tert*-butoxycarbonylamino)pyrrolidine-1-carboxylate

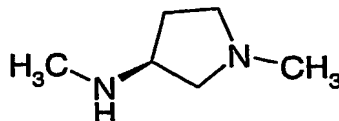
(3*S*)-3-(*tert*-Butoxycarbonylamino)pyrrolidine (1g, 5.37mmol) and triethylamine
 5 (1.38mL, 10.00mmol) were dissolved in dichloromethane (15mL) and the
 solution stirred at room temperature for 10 minutes. The solution was then
 treated with di-*tert*-butyl dicarbonate (1.75g, 8.00mmol) and the reaction mixture
 stirred at room temperature for 18 hours. The reaction mixture was concentrated
 10 *in vacuo* and the residue purified by column chromatography on silica gel eluting
 with pentane:ethyl acetate 80:20 to yield the title product as a white solid, 1.25g.
¹H-NMR (CDCl₃, 400MHz) δ: 1.39 (s, 18H), 1.81 (m, 1H), 2.15 (m, 1H), 3.13 (m,
 1H), 3.40 (m, 2H), 3.58 (m, 1H), 4.17 (m, 1H), 4.62 (m, 1H). MS ES+ m/z 309
 [MNa]⁺

15

Preparation 61*tert*-Butyl (3*R*)-3-(*tert*-butoxycarbonylamino)pyrrolidine-1-carboxylate

This compound was prepared by a method similar to that described for
 preparation 60 using (3*R*)-3-(*tert*-butoxycarbonylamino)pyrrolidine.
 20 ¹H-NMR (CDCl₃, 400MHz) δ: 1.37 (s, 18H), 1.79 (m, 1H), 2.15 (m, 1H), 3.13 (m,
 1H), 3.40 (m, 2H), 3.58 (m, 1H), 4.16 (m, 1H), 4.62 (m, 1H). MS ES+ m/z 309
 [MNa]⁺

25

Preparation 62(3*S*)-*N*,1-Dimethyl-3-pyrrolidinylamine

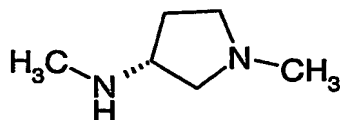
A solution of lithium aluminiumhydride (17mL, 16.89mmol) in tetrahydrofuran (10mL) was added dropwise to a stirring solution of the pyrrolidine of preparation 60 (600mg, 2.09mmol) in tetrahydrofuran (10mL) at 0°C. The reaction mixture was allowed to warm to room temperature and then heated to reflux for 5 hours.

5 The reaction mixture was cooled to 0°C with an ice bath and then quenched by addition of sodium sulphate solution. The reaction mixture was diluted with ethyl acetate (100mL) and the aqueous washed with additional ethyl acetate. The combined organics were dried over magnesium sulphate and concentrated *in vacuo* to yield the title product, 60mg.

10 ¹H-NMR (CD₃OD, 400MHz) δ: 2.25-2.46 (m, 4H), 2.75 (s, 3H), 3.02 (s, 3H), 3.73-4.08 (m, 4H), . MS APCI+ m/z 115 [MH]⁺

Preparation 63

(3*R*)-N,1-Dimethyl-3-pyrrolidinylamine



15

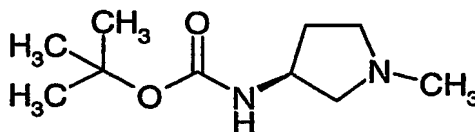
This compound was prepared by a method similar to that described for preparation 62 using the pyrrolidine of preparation 61.

¹H-NMR (CD₃OD, 400MHz) δ: 2.23-2.47 (m, 4H), 2.75 (s, 3H), 2.99 (s, 3H), 3.74-4.06 (m, 4H). MS APCI+ m/z 115 [MH]⁺

20

Preparation 64

tert-Butyl (3*S*)-(1-methyl-3-pyrrolidinyl)carbamate



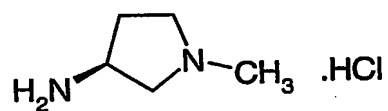
25 (3*S*)-3-(*tert*-Butoxycarbonylamino)pyrrolidine (2.0g, 10.75mmol) was dissolved in dichloromethane (100mL) and the solution treated with a 37% aqueous solution of formaldehyde (3.5mL, 43mmol). The solution was stirred for 30 minutes at room temperature and then treated with sodium triacetoxyborohydride (4.53g, 21.1mmol) over 15 minutes. The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with sodium

hydrogencarbonate solution (100mL) and the two phases separated. The organic layer was dried over magnesium sulphate and concentrated *in vacuo* to yield the title product.

¹H-NMR (CD₃OD, 400MHz) δ: 1.42 (s, 9H), 1.63 (m, 1H), 2.22 (m, 1H), 2.33 (s, 3H), 2.38 (m, 1H), 2.51 (m, 1H), 2.63 (m, 1H), 2.80 (m, 1H), 4.08 (m, 1H)

Preparation 65

(3S)-1-Methyl-3-pyrrolidinylamine hydrochloride

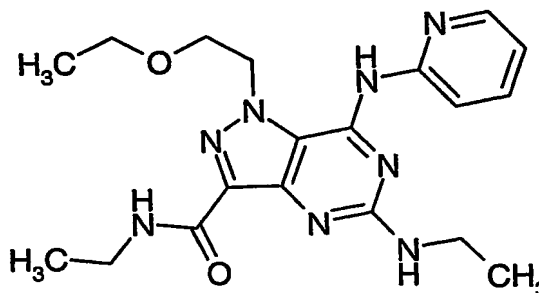


The product of preparation 64 (2.13g, 10.65mmol) was dissolved in a mixture of 30% trifluoroacetic acid (by volume) in dichloromethane (100mL) and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue taken up in methanol (50mL) and treated with 2M hydrogen chloride in ether (10mL). The solution was concentrated *in vacuo*, redissolved in methanol (50mL) and treated with additional 2M hydrogen chloride in ether (10mL). The solution was concentrated *in vacuo* and the residue triturated with ether to yield the title product.

¹H-NMR (CD₃OD, 400MHz) δ: 2.23 (m, 1H), 2.63 (m, 1H), 3.01 (s, 3H), 3.40-3.92 (m, 4H), 4.18 (m, 1H)

Example 1

1-(2-ethoxyethyl)-N-ethyl-5-(ethylamino)-7-(pyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide



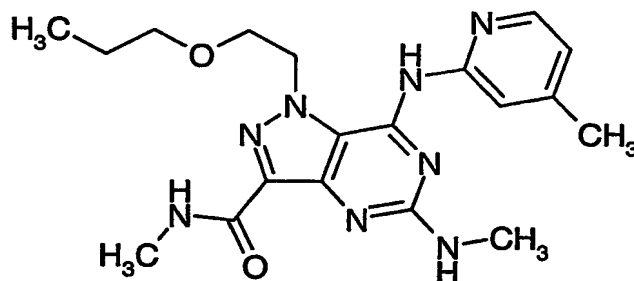
The ester of preparation 30 (80mg, 0.21mmol) was dissolved in dimethyl sulfoxide (1mL) and the solution treated with ethylamine (530μL, 1.05mmol)

and N-ethyldiisopropylamine (180 μ L, 0.98mmol). The reaction mixture was heated to 120°C for 18 hours and then treated with additional ethylamine (29 μ L, 0.53mmol) before being heated for a further 2 hours at 120°C. The reaction mixture was taken up in dichloromethane (100mL) and washed with water (3x150mL). The organics were combined, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonia 100:0:0 to 97:2:1 to yield the title product as a yellow oil, 20mg.

¹H-NMR (CD₃OD, 400MHz) δ : 1.07 (t, 3H), 1.27 (m, 6H), 3.41-3.60 (m, 6H), 3.90 (t, 2H), 4.81 (m, 2H), 7.06 (t, 1H), 7.78 (t, 1H), 8.28 (m, 1H), 8.55 (d, 1H). MS APCI+ m/z 399 [MH]⁺

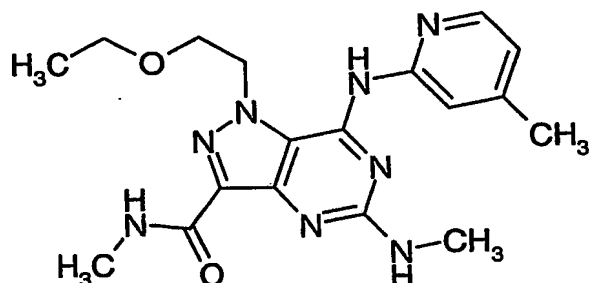
Example 2

N-Methyl-5-(methylamino)-7-(4-methylpyridin-2-ylamino)-1-(2-propoxyethyl)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide



The title compound was prepared by a method similar to that described for example 1 using an 8M solution of methylamine in ethanol and the ester of preparation 28

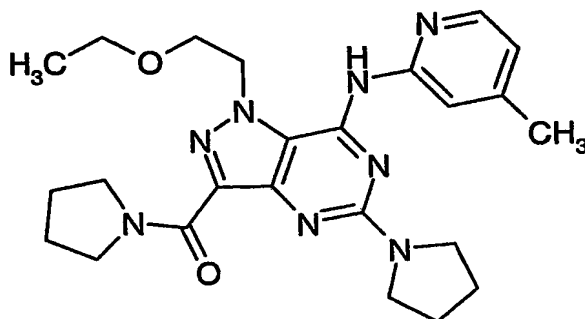
¹H-NMR (CD₃OD, 400MHz) δ : 0.77 (t, 3H), 1.46 (m, 2H), 2.54 (s, 3H), 2.93 (s, 3H), 3.10 (s, 3H), 3.41 (m, 2H), 3.93 (m, 2H), 5.03 (m, 2H), 7.13 (m, 1H), 8.11 (m, 2H). MS ES+ m/z 399 [MH]⁺

Example 31-(2-Ethoxyethyl)-N-methyl-5-(methylamino)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

- 5 The title compound was prepared by a method similar to that described for example 1 using an 8M solution of methylamine in ethanol and the ester of preparation 25.

¹H-NMR (CD₃OD, 400MHz) δ: 1.18 (t, 3H), 2.40 (s, 3H), 3.00 (s, 3H), 3.05(s, 3H), 3.63 (m, 2H), 3.97 (m, 2H), 4.77 (m, 2H), 6.90 (d, 1H), 8.20 (d, 1H), 8.27 (m, 1H),. MS APCI+ m/z 385 [MH]⁺

10

Example 4[1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-5-(pyrrolidin-1-yl)-3-(pyrrolidin-1-carbonyl)-1H-pyrazolo[4,3-d]pyrimidine]

15

- The ester of preparation 25 (100mg, 0.25mmol) was dissolved in a mixture of N-ethyldiisopropylamine (220μL, 1.25mmol), pyrrolidine (60μL, 0.75mmol) and dimethyl sulfoxide (1mL) and the reaction mixture heated to 120°C for 18 hours. The reaction mixture was concentrated *in vacuo*, the residue was taken up in dichloromethane (100mL) and washed with water (3x100mL). The organics were dried over magnesium sulphate and concentrated *in vacuo*. The residue
- 20

was purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 90:10 to yield the title product.

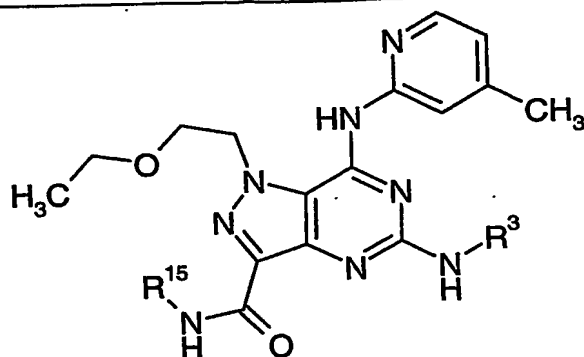
¹H-NMR (CD₃OD, 400MHz) δ : 1.10 (t, 3H), 1.90-2.08 (m, 8H), 2.40 (s, 3H), 3.62 (m, 8H), 3.80 (t, 2H), 3.98 (t, 2H), 4.80 (m, 2H), 6.98 (d, 1H), 8.18 (d, 1H), 8.57 (s, 1H). MS APCI+ m/z 465 [MH]⁺

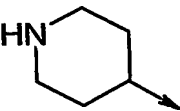
Examples 5 to 49

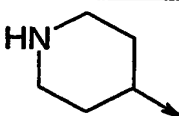
The compounds of Examples 5 to 49 were prepared by the following general method:

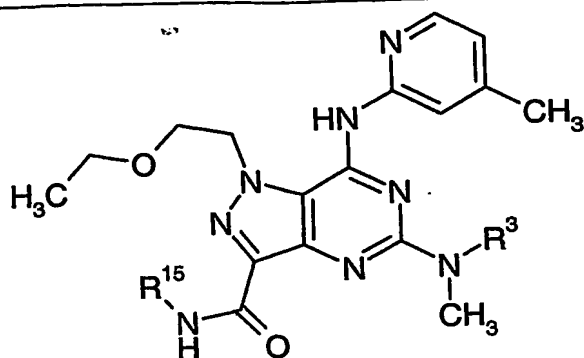
10

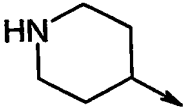
The appropriate carboxylic acid of preparations 34, 35, 36, 58, and 59 (1eq) was dissolved in 1-methyl-2-pyrrolidinone (6mLmmol⁻¹) and the solution treated with N,N'-carbonyldiimidazole (1.1eq) and N-ethyldiisopropylamine (1.1eq). The mixture was stirred at room temperature for 30 minutes and then the appropriate
15 HNR¹⁵R¹⁶ amine (1.1-1.2 eq) added and the reaction mixture stirred at room temperature for 1 hour. The appropriate HNR³R⁴ amine (2.5-3eq) was then added and the reaction mixture stirred at 120°C for 5 hours. The reaction mixture was concentrated in vacuo and the residue purified by HPLC on a Phenomenex Luna[®] C₁₈ 5 μ m column, eluting with 0.1% diethylamine in water:acetonitrile 95:5
20 to 5:95, or, in the case of examples 14, 20, 21, 22, 23, 27, 28, 33, 36, 37, 42, 44, 46 and 48, by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 95:5) to yield the title product.

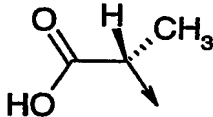
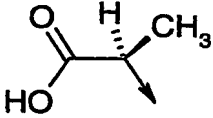


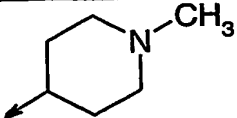
| Ex | |
|----|---|
| 5* | $R^3 = -CH_3$; $R^{15} = -(CH_2)_2NHCH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 2.39 (s, 3H), 2.48 (s, 3H), 2.92 (t, 2H), 3.00 (s, 3H), 3.58 (m, 2H), 3.68 (t, 2H), 3.94 (t, 2H), 4.79 (t, 2H), 6.93 (d, 1H), 8.15 (d, 1H), 8.42 (m, 1H). MS ES+ m/z 428 $[MH]^+$ |
| 6 | $R^3 = -CH_3$; $R^{15} = -(CH_2)_2N(CH_3)_2$ 1H -NMR (CD_3OD , 400MHz) δ : 1.06 (t, 3H), 2.31 (s, 6H), 2.42 (s, 3H), 2.64 (t, 2H), 3.02 (s, 3H), 3.58 (m, 2H), 3.62 (t, 2H), 3.93 (t, 2H), 4.78 (m, 2H), 6.94 (d, 1H), 8.13 (m, 1H), 8.43 (s, 1H). MS ES+ m/z 442 $[MH]^+$ |
| 7* | $R^3 = -CH_3$; $R^{15} = $  1H -NMR (CD_3OD , 400MHz) δ : 1.09 (t, 3H), 1.67 (m, 2H), 2.16 (m, 2H), 2.41 (s, 3H), 2.88 (m, 2H), 3.00 (s, 3H), 3.20 (m, 2H), 3.58 (m, 2H), 3.92 (t, 2H), 4.13 (m, 1H), 4.79 (t, 2H), 6.93 (d, 1H), 8.12 (d, 1H), 8.42 (m, 1H). MS ES+ m/z 454.3 $[MH]^+$ |
| 8 | $R^3 = -CH_2CH_3$; $R^{15} = -CH_2CH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.08 (t, 3H), 1.30 (m, 6H), 2.42 (s, 3H), 3.42-3.62 (m, 6H), 3.94 (t, 2H), 4.79 (t, 2H), 6.94 (d, 1H), 8.14 (d, 1H), 8.44 (s, 1H). MS ES+ m/z 413 $[MH]^+$ |
| 9* | $R^3 = -CH_2CH_3$; $R^{15} = -(CH_2)_2NH_2$ 1H -NMR (CD_3OD , 400MHz) δ : 1.11 (t, 3H), 1.32 (t, 3H), 2.43 (s, 3H), 2.93 (t, 2H), 3.49 (m, 2H), 3.56 (m, 4H), 3.95 (t, 2H), 4.79 (t, 2H), 6.93 (d, 1H), 8.14 (d, 1H), 8.42 (m, 1H). MS ES+ m/z 428 $[MH]^+$ |

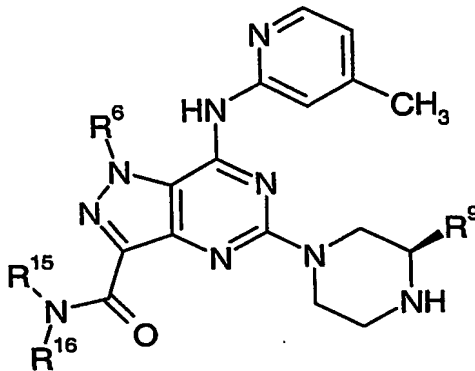
| | |
|-----|--|
| 10* | $R^3 = -CH_2CH_3$; $R^{15} = -(CH_2)_2NHCH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.09 (t, 3H), 1.28 (t, 3H), 2.41 (s, 3H), 2.46 (s, 3H), 2.90 (t, 2H), 3.50 (m, 2H), 3.59 (m, 2H), 3.64 (t, 2H), 3.94 (t, 2H), 4.79 (t, 2H), 6.93 (d, 1H), 8.14 (d, 1H), 8.42 (m, 1H). MS ES+ m/z 442 $[MH]^+$ |
| 11 | $R^3 = -CH_2CH_3$; $R^{15} = -(CH_2)_2N(CH_3)_2$ 1H -NMR (CD_3OD , 400MHz) δ : 1.07 (t, 3H), 1.26 (t, 3H), 2.30 (s, 6H), 2.41 (s, 3H), 2.62 (t, 2H), 3.42-3.70 (m, 6H), 3.92 (t, 2H), 4.78 (m, 2H), 6.93 (d, 1H), 8.14 (m, 1H), 8.42 (m, 1H). MS APCI+ m/z 456 $[MH]^+$ |
| 12* | $R^3 = -CH_2CH_3$; $R^{15} = $  1H -NMR (CD_3OD , 400MHz) δ : 1.12 (t, 3H), 1.28 (t, 3H), 1.64 (m, 2H), 2.14 (m, 2H), 2.43 (s, 3H), 2.88 (m, 2H), 3.20 (m, 2H), 3.47 (m, 2H), 3.60 (m, 2H), 3.95 (t, 2H), 4.15 (m, 1H), 4.79 (t, 2H), 6.94 (br, 1H), 8.13 (m, 1H), 8.43 (m, 1H). MS ES+ m/z 468 $[MH]^+$ |
| *13 | $R^3 = -CH(CH_3)_2$; $R^{15} = -(CH_2)_2NH_2$ 1H -NMR (CD_3OD , 400MHz) δ : 1.08 (t, 3H), 1.29 (d, 6H), 2.41 (s, 3H), 2.94 (t, 2H), 3.58 (m, 4H), 3.94 (t, 2H), 4.18 (m, 1H), 4.79 (t, 2H), 6.93 (d, 1H), 8.14 (d, 1H), 8.42 (m, 1H). MS ES+ m/z 442 $[MH]^+$ |



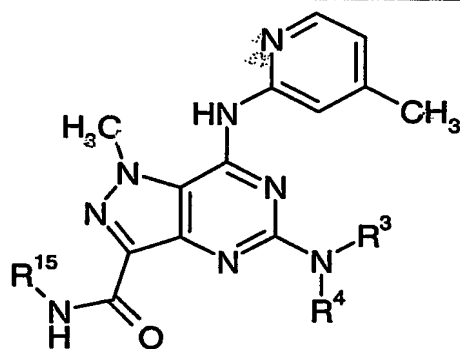
| Ex | |
|-----|---|
| 14 | $R^3 = -CH_3$; $R^{15} = -CH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 2.41 (s, 3H), 3.04 (s, 3H), 3.24 (s, 6H), 3.60 (m, 2H), 3.92 (t, 2H), 4.79 (t, 2H), 6.95 (d, 1H), 8.18 (d, 1H), 8.37 (s, 1H). MS ES+ m/z 399 $[MH]^+$ |
| 15* | $R^3 = -CH_3$; $R^{15} = -(CH_2)_2NH_2$ 1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 2.40 (s, 3H), 2.94 (t, 2H), 3.28 (s, 6H), 3.60 (m, 4H), 3.92 (t, 2H), 4.79 (t, 2H), 6.94 (d, 1H), 8.16 (d, 1H), 8.37 (m, 1H). MS ES+ m/z 428 $[MH]^+$ |
| 16* | $R^3 = -CH_3$; $R^{15} = -(CH_2)_2NHCH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.08 (t, 3H), 2.39 (s, 3H), 2.45 (s, 3H), 2.88 (t, 2H), 3.26 (s, 6H), 3.59 (m, 2H), 3.64 (t, 2H), 3.93 (t, 2H), 4.79 (t, 2H), 6.94 (d, 1H), 8.18 (d, 1H), 8.36 (m, 1H). MS ES+ m/z 442 $[MH]^+$ |
| 17 | $R^3 = -CH_3$; $R^{15} = -(CH_2)_2N(CH_3)_2$ 1H -NMR ($CDCl_3$, 400MHz) δ : 1.05 (t, 3H), 2.32 (m, 6H), 2.35 (s, 3H), 2.64 (m, 2H), 3.24 (s, 6H), 3.60 (m, 2H), 3.72 (m, 2H), 3.96 (t, 2H), 4.78 (m, 2H), 6.92 (d, 1H), 8.18 (d, 1H), 8.34 (s, 1H), 9.12 (m, 1H), 9.78 (s, 1H). MS APCI+ m/z 456 $[MH]^+$ |
| 18* | $R^3 = -CH_3$; $R^{15} = $  1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 1.60 (m, 2H), 2.12 (m, 2H), 2.40 (s, 3H), 2.82 (m, 2H), 3.15 (m, 2H), 3.28 (s, 6H), 3.60 (m, 2H), 3.93 (t, 2H), 4.10 (m, 1H), 4.79 (t, 2H), 6.96 (d, 1H), 8.17 (d, 1H), 8.37 (m, 1H). MS ES+ m/z 468 $[MH]^+$ |

| | |
|-----|--|
| 19 | $R^3 = -CH_3$; $R^{15} = -(CH_2)_2OCH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.11 (t, 3H), 2.40 (s, 3H), 3.28 (s, 6H), 3.42 (s, 3H), 3.60 (m, 4H), 3.67 (t, 2H), 3.93 (t, 2H), 4.79 (t, 2H), 6.93 (d, 1H), 8.17 (d, 1H), 8.37 (s, 1H). MS ES+ m/z 443 $[MH]^+$ |
| 20* | $R^3 = -CH_3$; $R^{15} = -CH_2CO_2H$ 1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 2.52 (s, 3H), 3.30 (s, 6H), 3.57 (q, 2H), 3.99 (t, 2H), 4.17 (s, 3H), 5.05 (t, 2H), 7.18 (d, 1H), 8.02 (s, 1H), 8.18 (d, 1H). MS APCI+ m/z 443 $[MH]^+$ |
| 21* | $R^3 = -CH_3$; $R^{15} = $  1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 1.57 (d, 3H), 2.51 (s, 3H), 3.30 (s, 6H), 3.48 (q, 2H), 3.99 (t, 2H), 4.63 (q, 1H), 5.02 (t, 2H), 7.18 (d, 1H), 8.02 (s, 1H), 8.17 (d, 1H). MS APCI+ m/z 457 $[MH]^+$ |
| 22* | $R^3 = -CH_3$; $R^{15} = $  1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 1.57 (d, 3H), 2.51 (s, 3H), 3.30 (s, 6H), 3.57 (q, 2H), 3.99 (t, 2H), 4.62 (q, 1H), 5.02 (t, 2H), 7.18 (d, 1H), 8.01 (s, 1H), 8.18 (d, 1H). MS APCI+ m/z 457 $[MH]^+$ |
| 23* | $R^3 = -CH_3$; $R^{15} = -(CH_2)_2CO_2H$ 1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 2.50 (s, 3H), 2.65 (t, 2H), 3.30 (s, 6H), 3.57 (q, 2H), 3.65 (t, 2H), 3.98 (t, 2H), 4.99 (t, 2H), 7.18 (d, 1H), 8.01 (s, 1H), 8.18 (d, 1H). MS APCI+ m/z 457 $[MH]^+$ |
| 24* | $R^3 = -CH_2CH_3$; $R^{15} = -(CH_2)_2NH_2$ 1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 1.24 (t, 3H), 2.40 (s, 3H), 2.94 (t, 2H), 3.23 (s, 3H), 3.60 (m, 4H), 3.77 (m, 2H), 3.96 (t, 2H), 4.79 (t, 2H), 6.97 (d, 1H), 8.17 (d, 1H), 8.34 (m, 1H). MS ES+ m/z 442 $[MH]^+$ |
| 25* | $R^3 = -CH(CH_3)_2$; $R^{15} = -(CH_2)_2NH_2$ 1H -NMR (CD_3OD , 400MHz) δ : 1.12 (t, 3H), 1.27 (d, 6H), 2.40 (s, 3H), 2.95 (t, 2H), 3.07 (s, 3H), 3.60 (m, 4H), 3.93 (t, 2H), 4.79 (t, 2H), 5.09 (m, 1H), 6.95 (d, 1H), 8.16 (d, 1H), 8.30 (m, 1H). MS ES+ m/z 456 $[MH]^+$ |

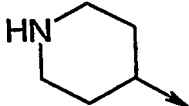
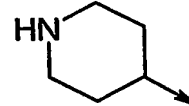
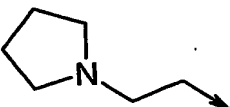
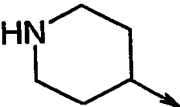
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| 26 | $R^3 = $  $; R^{15} = -CH_3$ 1H -NMR (CD ₃ OD, 400MHz) δ : 1.10 (t, 3H), 1.79 (m, 2H), 1.94 (m, 2H), 2.20 (m, 2H), 2.34 (s, 3H), 2.44 (s, 3H), 3.05 (m, 2H), 3.07 (s, 3H), 3.12 (s, 3H), 3.62 (q, 2H), 3.93 (t, 2H), 4.68 (m, 1H), 4.80 (t, 2H), 6.97 (d, 1H), 8.18 (m, 2H). MS ES+ m/z 482 [MH] ⁺ |
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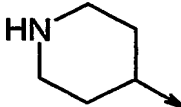
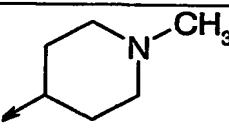
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| Ex | |
| 27* | $R^6 = -CH_3; R^9 = H; R^{15} = -CH_3, R^{16} = H$ 1H -NMR (CD ₃ OD, 400MHz) δ : 2.41 (s, 3H), 3.02 (m, 4H), 3.04 (s, 3H), 3.87 (m, 4H), 4.36 (s, 3H), 6.99 (m, 1H), 7.96 (m, 1H), 8.18 (m, 1H). MS APCI+ m/z 382 [MH] ⁺ |
| 28 | $R^6 = -CH_3; R^9 = -CH_3; R^{15} = -CH_3, R^{16} = H$ 1H -NMR (CD ₃ OD, 400MHz) δ : 1.18 (d, 3H), 2.43 (s, 3H), 2.70 (m, 2H), 2.87 (m, 2H), 3.04 (s, 3H), 3.08 (m, 1H), 4.37 (s, 3H), 4.55 (m, 2H), 7.01 (m, 1H), 7.67 (m, 1H), 8.19 (m, 1H). MS APCI+ m/z 396 [MH] ⁺ |
| 29* | $R^6 = -(CH_2)_2OCH_2CH_3; R^9 = H; R^{15} = -CH_3, R^{16} = H$ 1H -NMR (CD ₃ OD, 400MHz) δ : 1.12 (t, 3H), 2.40 (s, 3H), 2.96 (t, 4H), 3.06 (s, 3H), 3.62 (q, 2H), 3.84 (t, 4H), 3.93 (t, 2H), 4.80 (t, 2H), 6.96 (d, 1H), 8.05 (m, 2H). MS ES+ m/z 440 [MH] ⁺ |

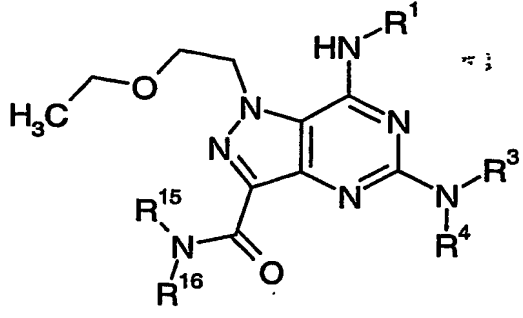
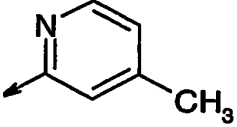
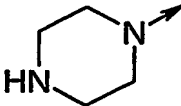
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| 30 | $R^6 = -(CH_2)_2OCH_2CH_3$; $R^9 = -CH_3$; $R^{15} = -CH_3$, $R^{16} = H$ 1H -NMR (CD_3OD , 400MHz) δ : 1.15 (t, 3H), 1.19 (d, 3H), 2.40 (s, 3H), 2.70 (m, 1H), 2.76 (m, 2H), 3.06 (s, 3H), 3.08 (m, 3H), 3.62 (m, 2H), 3.94 (t, 2H), 4.60 (m, 2H), 4.80 (t, 2H), 6.97 (d, 1H), 8.18 (m, 2H). MS ES+ m/z 454 $[MH]^+$ |
| 31 | $R^6 = -(CH_2)_2OCH_2CH_3$; $R^9 = -CH_3$; $R^{15} = -CH_3$, $R^{16} = -CH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.14 (t, 3H), 1.18 (d, 3H), 2.42 (s, 3H), 2.64 (m, 1H), 2.83 (m, 2H), 2.94-3.04 (m, 2H), 3.16 (s, 3H), 3.21 (s, 3H), 3.62 (q, 2H), 3.93 (t, 2H), 4.60 (m, 2H), 4.78 (t, 2H), 6.95 (d, 1H), 8.18 (d, 1H), 8.20 (s, 1H). MS ES+ m/z 468 $[MH]^+$ |
| 32 | $R^6 = -(CH_2)_2OCH_2CH_3$; $R^9 = -CH_3$; $R^{15} = -CH_2CH_3$, $R^{16} = H$ 1H -NMR ($DMSO-D_6$, 400MHz) δ : 1.02 (m, 6H), 1.18 (t, 3H), 2.34 (s, 3H), 2.53 (t, 2H), 2.70 (m, 2H), 2.84-2.93 (m, 2H), 3.38 (m, 2H), 3.52 (m, 2H), 3.82 (t, 2H), 4.58 (m, 2H), 4.72 (t, 2H), 6.94 (d, 1H), 8.00 (s, 1H), 8.19 (d, 1H), 8.53 (m, 1H). MS ES+ m/z 468 $[MH]^+$ |

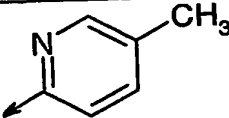
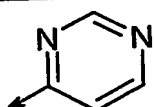
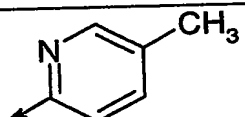
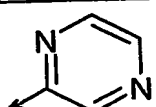


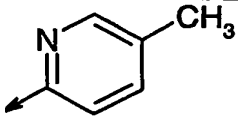
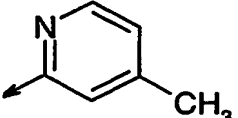
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| Ex | |
| 33 | $R^3 = -CH_3$; $R^4 = H$; $R^{15} = -CH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 2.40 (s, 3H), 2.98 (s, 3H), 3.01 (s, 3H), 4.36 (s, 3H), 6.90 (d, 1H), 7.72 (s, 1H), 8.09 (d, 1H). MS APCI+ m/z 327 $[MH]^+$ |

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| 34* | $R^3 = -CH_2CH_3$; $R^4 = H$; $R^{15} = $  <p>1H-NMR (CD_3OD, 400MHz) δ: 1.31 (t, 3H), 1.59 (m, 2H), 2.07 (m, 2H), 2.40 (s, 3H), 2.80 (m, 2H), 3.11 (m, 2H), 4.08 (m, 1H), 4.37 (s, 3H), 6.90 (m, 2H), 8.10 (m, 1H). MS ES+ m/z 410 $[MH]^+$</p> |
| 35* | $R^3 = -CH(CH_3)_2$; $R^4 = H$; $R^{15} = $  <p>1H-NMR (CD_3OD, 400MHz) δ: 1.28 (d, 6H), 1.59 (m, 2H), 2.11 (m, 2H), 2.41 (s, 3H), 2.80 (m, 2H), 3.30 (m, 1H), 4.09 (m, 1H), 4.37 (s, 3H), 6.97 (m, 1H), 8.17 (m, 2H). MS ES+ m/z 424 $[MH]^+$</p> |
| 36 | $R^3 = -CH_3$; $R^4 = -CH_3$; $R^{15} = -CH_3$ 1H -NMR ($DMSO-D_6$, 400MHz) δ : 2.33 (s, 3H), 2.89 (d, 3H), 3.16 (s, 6H), 4.28 (s, 3H), 6.94 (m, 1H), 8.19 (d, 1H), 8.43 (m, 1H). MS APCI+ m/z 341 $[MH]^+$ |
| 37 | $R^3 = -CH_3$; $R^4 = -CH_3$; $R^{15} = -(CH_2)_2N(CH_3)_2$ 1H -NMR (CD_3OD , 400MHz) δ : 2.35 (s, 3H), 2.42 (t, 2H), 2.69 (m, 6H), 3.18 (s, 6H), 3.75 (t, 2H), 4.32 (s, 3H), 6.93 (m, 2H), 8.09 (m, 1H). MS APCI+ m/z 398 $[MH]^+$ |
| 38 | $R^3 = -CH_3$; $R^4 = -CH_3$; $R^{15} = $  <p>1H-NMR (CD_3OD, 400MHz) δ: 1.83 (m, 4H), 2.39 (s, 3H), 2.67 (m, 4H), 2.80 (t, 2H), 3.21 (s, 6H), 3.64 (t, 2H), 4.34 (s, 3H), 6.98 (m, 1H), 8.15 (m, 2H). MS ES+ m/z 424 $[MH]^+$</p> |
| 39* | $R^3 = -CH_3$; $R^4 = -CH_3$; $R^{15} = $  <p>1H-NMR (CD_3OD, 400MHz) δ: 1.57 (m, 2H), 2.10 (m, 2H), 2.40 (s, 3H), 2.82 (m, 2H), 3.13 (m, 2H), 3.23 (s, 6H), 4.08 (m, 1H), 4.35 (s, 3H), 6.96 (m, 1H), 8.15 (m, 2H). MS ES+ m/z 410 $[MH]^+$</p> |

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| 40* | $R^3 = -CH(CH_3)_2$; $R^4 = -CH_3$; $R^{15} = -(CH_2)_2NH_2$ 1H -NMR (CD_3OD , 400MHz) δ : 1.28 (d, 6H), 2.41 (s, 3H), 2.99 (t, 2H), 3.07 (s, 3H), 3.30 (m, 1H), 3.63 (t, 2H), 4.37 (s, 3H), 6.97 (m, 1H), 8.17 (m, 1H), 8.54 (d, 1H). MS ES+ m/z 398 $[MH]^+$ |
| 41* | $R^3 = -CH(CH_3)_2$; $R^4 = -CH_3$; $R^{15} = $  1H -NMR (CD_3OD , 400MHz) δ : 1.33 (d, 6H), 1.60 (m, 2H), 2.11 (m, 2H), 2.40 (m, 3H), 2.82 (m, 2H), 3.14 (m, 2H), 4.09 (m, 1H), 4.38 (s, 3H), 6.89 (m, 1H), 8.10 (m, 1H). MS ES+ m/z 438 $[MH]^+$ |
| 42 | $R^3 = $  ; $R^4 = -CH_3$; $R^{15} = -CH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.86 (m, 2H), 1.97 (m, 2H), 2.38 (m, 4H), 2.45 (s, 3H), 3.09 (s, 3H), 3.12 (s, 3H), 3.17 (m, 1H), 4.36 (s, 3H), 6.57 (s, 1H), 7.00 (m, 1H), 8.19 (m, 1H). MS APCI+ m/z 424 $[MH]^+$ |

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| Ex | |
| 43* | $R^1 = $  ; $R^3 = -CH_3$; $R^4 = H$; $-NR^{15}R^{16} = $  1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 2.42 (s, 3H), 2.93 (m, 4H), 2.98 (s, 3H), 3.60 (m, 2H), 3.64 (m, 2H), 3.78 (m, 2H), 3.92 (t, 2H), 4.78 (m, 2H), 6.97 (m, 1H), 8.15 (m, 1H), 8.42 (s, 1H). MS ES+ m/z 440 $[MH]^+$ |

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| 44 | <p> $R^1 =$  $; R^3 = -CH_3; R^4 = -CH_3; R^{15} = -(CH_2)_2OCH_3; R^{16} = H$ </p> <p> 1H-NMR (CD_3OD, 400MHz) δ: 1.10 (t, 3H), 1.30 (t, 3H), 2.34 (s, 3H), 3.42 (s, 3H), 3.50 (q, 2H), 3.60 (m, 4H) 3.69 (m, 2H), 3.96 (m, 2H), 4.99 (m, 2H), 7.64 (m, 1H), 8.16 (m, 1H), 8.49 (m, 1H). MS APCI+ m/z 443 $[MH]^+$ </p> |
| 45 | <p> $R^1 =$  $; R^3 = -CH_3; R^4 = -CH_3; R^{15} = -(CH_2)_2OCH_3; R^{16} = H$ </p> <p> 1H-NMR (CD_3OD, 400MHz) δ: 1.21 (t, 3H), 3.34 (s, 3H), 3.34 (s, 6H), 3.69 (m, 6H), 3.96 (t, 2H), 4.81 (t, 2H), 8.39 (d, 1H), 8.61 (d, 1H), 8.83 (s, 1H). MS ES+ m/z 430 $[MH]^+$ </p> |
| 46 | <p> $R^1 =$  $; R^3 = -CH_2CH_3; R^4 = H; R^{15} = -CH_2CH_3; R^{16} = H$ </p> <p> 1H-NMR (CD_3OD, 400MHz) δ: 1.12 (t, 3H), 1.30 (m, 6H), 2.36 (s, 3H), 3.48 (q, 2H), 3.56 (m, 2H), 3.60 (m, 2H) 3.69 (q, 2H), 3.97 (m, 2H), 4.78 (m, 2H), 7.68 (m, 1H), 8.17 (m, 1H), 8.50 (m, 1H). MS APCI+ m/z 413 $[MH]^+$ </p> |
| 47 | <p> $R^1 =$  $; R^3 = -CH_2CH_3; R^4 = H; R^{15} = -CH_2CH_3; R^{16} = H$ </p> <p> 1H-NMR (CD_3OD, 400MHz) δ: 1.20 (t, 3H), 1.31 (d, 6H), 3.53 (m, 4H), 3.65 (q, 2H), 3.96 (t, 2H) 4.80 (t, 2H), 8.27 (d, 1H), 8.37 (d, 1H), 9.71 (s, 1H). MS APCI+ m/z 400 $[MH]^+$ </p> |

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| 48 | $R^1 = $  $; R^3 = -CH_2CH_3; R^4 = H; R^{15} = -(CH_2)_2OCH_3;$ $R^{16} = H$ 1H -NMR (CD ₃ OD, 400MHz) δ : 1.12 (t, 3H), 1.30 (t, 3H), 2.32 (s, 3H), 3.42 (s, 3H), 3.49 (q, 2H), 3.60 (m, 4H) 3.69 (q, 2H), 3.96 (m, 2H), 4.79 (m, 2H), 7.62 (m, 1H), 8.16 (m, 1H), 8.44 (m, 1H). MS APCI+ m/z 443 [MH] ⁺ |
| 49* | $R^1 = $  $; R^3 = -CH_2CH_3; R^4 = -CH_2CH_3;$ $R^{15} = -(CH_2)_2NH_2; R^{16} = H$ 1H -NMR (CD ₃ OD, 400MHz) δ : 1.12 (t, 3H), 1.30 (t, 6H), 2.42 (s, 3H), 2.94 (t, 2H), 3.60 (m, 4H), 3.73 (m, 4H), 3.95 (t, 2H), 4.79 (t, 2H), 6.96 (d, 1H), 8.16 (d, 1H), 8.38 (m, 1H). MS ES+ m/z 456 [MH] ⁺ |

Notes on Examples 5 – 49

- Examples 5, 6, 7, 14, 26, 27, 28, 29, 30, 33, 36, 42 and 43 used an 8M solution of methylamine in ethanol to provide the HNR¹⁵R¹⁶ and / or HNR³R⁴ amine.
- Examples 27 and 29 used *tert*-butyl piperazine-1-carboxylate as the HNR³R⁴ amine.
- Examples 18 and 43 used *tert*-butyl piperazine-1-carboxylate as the HNR¹⁵R¹⁶ amine.
- Examples 7, 12, 34, 35, 39 and 41 used *tert*-butyl 4-aminopiperidine-1-carboxylate as the HNR¹⁵R¹⁶ amine.
- Examples 9, 13, 15, 24, 25, 40 and 49 used *tert*-butyl (2-aminoethyl)-carbamate as the HNR¹⁵R¹⁶ amine.
- Examples 5, 10 and 16 used *tert*-butyl *N*-(2-aminoethyl)-*N*-methylcarbamate as the HNR¹⁵R¹⁶ amine.
- Example 20 used glycine *tert*-butyl ester as the HNR¹⁵R¹⁶ amine.
- Example 21 used L-alanine *tert*-butyl ester (Chem. Pharm. Bull., 1978, 26 (3), 803-808) as the HNR¹⁵R¹⁶ amine.

- Example 22 used D-alanine *tert*-butyl ester (Chem. Pharm. Bull., 1978, 26 (3), 803-808) as the HNR¹⁵R¹⁶ amine.
- Example 23 used β -alanine *tert*-butyl ester (ChemBioChem, 2001, 2, 171-179, compound 9) as the HNR¹⁵R¹⁶ amine.

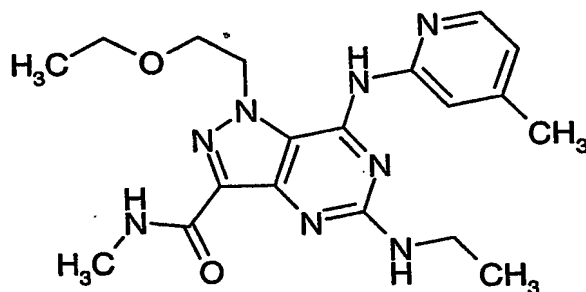
5

*Prior to column chromatography, these examples were treated with a solution of trifluoroacetic acid in dichloromethane (0.5mL), stirred at room temperature for 6 hours and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel as described above.

10

Example 50

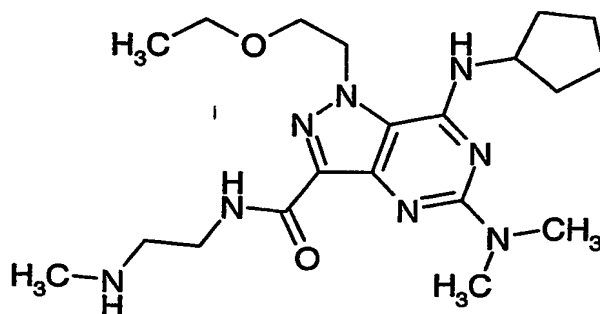
1-(2-Ethoxyethyl)-5-(ethylamino)-N-methyl-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide



- 15 The carboxylic acid of preparation 34 (50mg, 0.13mmol) was dissolved in 1-methyl-2-pyrrolidinone (1mL) and the solution treated with N,N'-carbonyldiimidazole (24mg, 0.15mmol) and N-ethyldiisopropylamine (25 μ L, 0.15mmol). The solution was then stirred at room temperature for 45 minutes before being treated with an 8M solution of methylamine in ethanol (19 μ L) and stirred at room temperature for 1 hour. Ethylamine (20.25mg, 0.45mmol) and additional N-ethyldiisopropylamine (25 μ L, 0.15mmol) was added and the reaction mixture heated to 120°C for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by HPLC on a Phenomenex Luna® C₁₈ 5 μ M column eluting with 0.1% diethylamine in water:acetonitrile 90:10 to 5:95 to yield the title product.

25

¹H-NMR (CD₃OD, 400MHz) δ : 1.08 (t, 3H), 1.29 (t, 3H), 2.43 (s, 3H), 3.02 (s, 3H), 3.49 (m, 2H), 3.60 (m, 2H), 3.94 (t, 2H), 4.79 (t, 2H), 6.95 (d, 1H), 8.16 (d, 1H), 8.43 (s, 1H). MS ES+ m/z 399 [MH]⁺

Example 517-(Cyclopentylamino)-5-(dimethylamino)-1-(2-ethoxyethyl)-N-(2-(methylamino)ethyl)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

5

A suspension of the carboxylic acid of preparation 38 (70mg, 0.2mmol) in dimethyl sulphoxide (2mL) was treated with N,N'-carbonyldiimidazole (35.6mg, 0.22mmol) and N-ethyldiisopropylamine (38μL, 0.22mmol) and sealed in a ReactiVial™ for 1 hour. After this time *tert*-butyl N-(2-aminoethyl)-N-

10 methylcarbamate (58μL, 0.32mmol) and further N,N'-carbonyldiimidazole (18mg, 0.11mmol) was added and stirring continued for 1 hour. The reaction mixture was dissolved in dichloromethane (30mL) and washed with water (2 x 20mL) then saturated brine (20mL). The organic layer was dried over magnesium sulphate and evaporated to give a colourless oil. The resulting oil was dissolved in

15 dimethyl sulphoxide (2mL) and treated with N-ethyldiisopropylamine (104μL, 0.6mmol) and dimethylamine solution 5.6 M in ethanol (107.2μL, 0.6mmol) before being sealed in a ReactiVial™ and heated to 120°C for 16 hours. The reaction mixture was again diluted with dichloromethane (30mL) and washed with water (2 x 20mL) and brine (20mL). The organic solution was dried over

20 magnesium sulphate and concentrated *in vacuo* to give a colourless oil. The resulting oil was re-dissolved in dichloromethane (1mL) and treated with trifluoroacetic acid (1mL) before stirring at room temperature for 2 hours. The reaction was concentrated *in vacuo* and the resulting oil was purified by column chromatography on silica gel eluting with

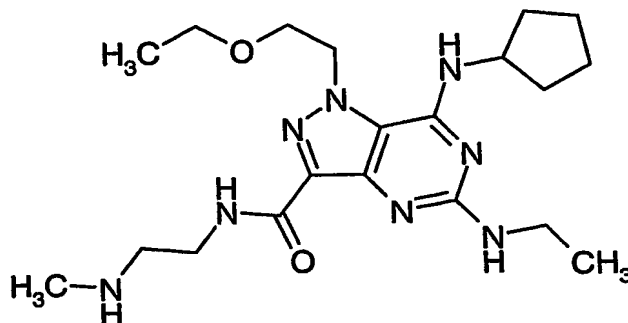
25 dichloromethane:methanol:0.88 ammonia 90:10:1 to give a white solid.

¹H-NMR (CDCl₃, 400MHz) δ: 1.10 (t, 3H), 1.51 (m, 2H), 1.64 (m, 2H), 1.75 (m, 2H), 2.16 (m, 2H), 2.59 (s, 3H), 3.07 (m, 2H), 3.21 (s, 6H), 3.47 (q, 2H), 3.75 (t,

2H), 3.85 (m, 2H), 4.36 (1, 2H), 4.62 (m, 2H) 6.74 (m, 1H), 9.03 (m, 1H). MS
APCI+ m/z 419 [MH]⁺

Example 52

5 7-(Cyclopentylamino)-1-(2-ethoxyethyl)-5-(ethylamino)-N-(2-(methylamino)ethyl)-
1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide



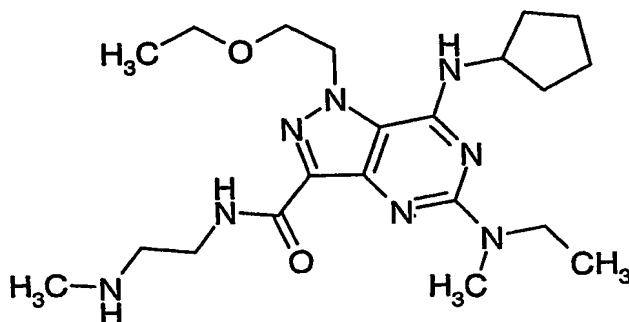
The title compound was prepared by a method similar to that described for
example 51 using *tert*-butyl *N*-(2-aminoethyl)-*N*-methylcarbamate and
10 ethylamine.

¹H-NMR (CDCl₃, 400MHz) δ: 1.13 (t, 3H), 1.24 (t, 3H), 1.60 (m, 2H), 1.68 (m,
2H), 1.80 (m, 2H), 2.15 (m, 2H), 2.46 (s, 3H), 2.87 (t, 2H), 3.42 (q, 2H), 3.53 (q,
2H), 3.63 (t, 2H), 3.86 (t, 2H), 4.43 (m, 1H), 4.62 (t, 2H); MS APCI+ m/z 419
[MH]⁺

15

Example 53

7-(Cyclopentylamino)-1-(2-ethoxyethyl)-5-(N-ethyl-N-methylamino)-N-(2-
(methylamino)ethyl)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide



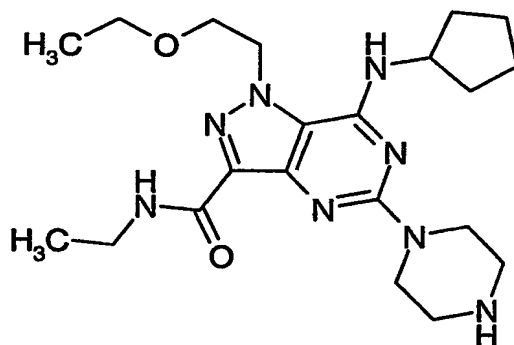
20 The title compound was prepared by a method similar to that described for
example 51 using *tert*-butyl *N*-(2-aminoethyl)-*N*-methylcarbamate and *N*-ethyl-
methylamine.

¹H-NMR (CD₃OD, 400MHz) δ: 1.13 (t, 3H), 1.19 (t, 3H), 1.60-1.71 (m, 4H), 1.80 (m, 2H), 2.17 (m, 2H), 2.43 (s, 3H), 2.85 (t, 2H) 3.17 (s, 3H), 3.53 (m, 4H), 3.63 (t, 2H), 3.72 (m, 2H), 4.42 (m, 1H), 4.63 (t, 2H). MS APCI+ m/z 433 [MH]⁺

5

Example 54

7-(Cyclopentylamino)-1-(2-ethoxyethyl)-N-ethyl-5-(piperazin-1-yl)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide



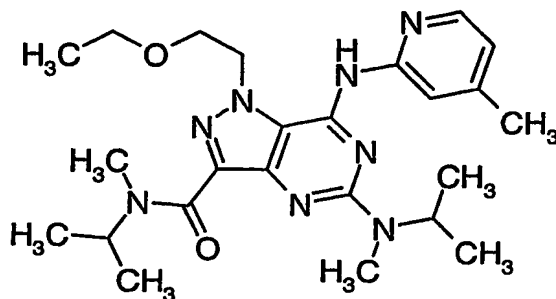
The title compound was prepared by a method similar to that described for example 51 using ethylamine and *tert*-butyl piperazine-1-carboxylate.

¹H-NMR (CD₃OD, 400MHz) δ: 1.11 (t, 3H), 1.27 (t, 3H), 1.66 (m, 4H), 1.80 (m, 2H), 2.18 (m, 2H), 2.93 (m, 4H) 3.53 (m, 2H), 3.81 (m, 4H) 3.85 (m, 2H), 4.41 (m, 1H), 4.63 (m, 2H). MS ES+ m/z 431 [MH]⁺

15

Example 55

1-(2-Ethoxyethyl)-N-isopropyl-5-(N-isopropyl-N-methylamino)-N-methyl-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide



The carboxylic acid of preparation 34 (440mg, 1.17mmol) and isopropylmethylamine (1.21mL, 11.67mmol) were dissolved in dimethyl sulphoxide (50mL) and the reaction mixture heated to 120°C for 12 hours. The

20

reaction mixture was concentrated *in vacuo* and the residue taken up in sodium carbonate solution (1mL) and concentrated *in vacuo*. The residue was treated with ammonium chloride solution (2mL) and concentrated *in vacuo*. The residue was triturated with acetone (5x30mL) and concentrated *in vacuo*. The residue

5 was purified by column chromatography on silica gel eluting with water:methanol 90:10 to 0:100. The crude product was washed with dichloromethane (2x100mL), dried over magnesium sulphate and concentrated *in vacuo* to yield the title product.

¹H-NMR (CD₃OD, 400MHz) δ : 1.10 (m, 3H), 1.30 (m, 12H), 2.40 (s, 3H), 3.03 (m, 5H), 3.30 (s, 3H), 3.61 (m, 2H), 3.90 (t, 2H), 4.78 (m, 2H), 6.97 (d, 1H), 8.18 (d, 1H), 8.35 (s, 1H). MS APCI+ m/z 469 [MH]⁺

10

Examples 56-64

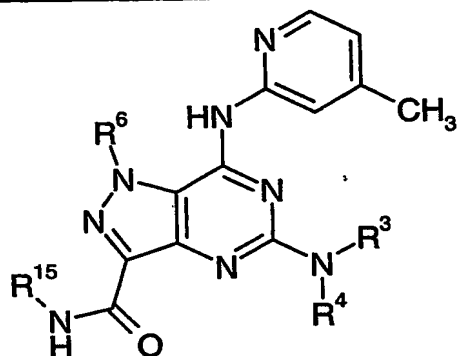
The compounds of Examples 56 to 64 were prepared by the following general method:

15

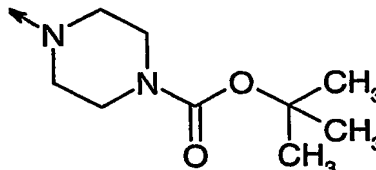
The appropriate amide of preparations 39, 40, 41, 42 and 43 (70mg, 0.18mmol) was dissolved in dimethylsulphoxide (1.4mL) and treated with N-ethyldiisopropylamine (0.16mL, 0.9mmol) and the appropriate HNR³R⁴ amine (0.92mmol). The reaction mixture was heated to 100°C for 18 hours before being allowed to cool and being washed with water (3x25mL) and dichloromethane (50mL). The organic layer was separated, dried with magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol

20

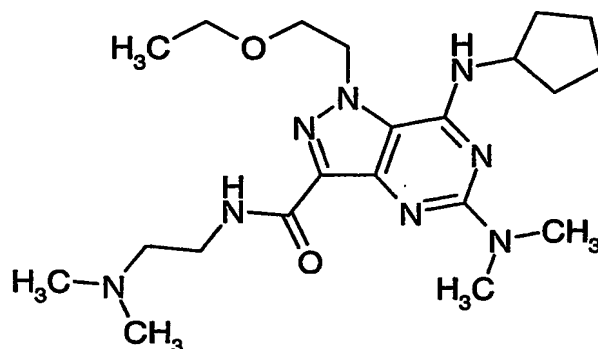
25 100:0 to 95:5 to yield the desired product.



| Ex | |
|----|--|
| 56 | $R^3 = -CH_3$; $R^4 = H$; $R^6 = -(CH_2)_2OCH_2CH_3$; $R^{15} = -(CH_2)_2OCH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 2.42 (s, 3H), 3.00 (s, 3H), 3.40 (s, 3H), 3.63 (m, 4H), 3.68 (m, 2H), 3.90 (t, 2H), 4.80 (t, 2H), 6.95 (d, 1H), 8.15 (d, 1H), 8.45 (s, 1H). MS APCI+ m/z 429 $[MH]^+$ |
| 57 | $R^3 = -CH_3$; $R^4 = -CH_3$; $R^6 = -CH(CH_3)_2$; $R^{15} = -(CH_2)_2N(CH_3)_2$ 1H -NMR (CD_3OD , 400MHz) δ : 0.93 (d, 6H), 2.31 (s, 6H), 2.38 (s, 3H), 2.62 (m, 2H), 3.25 (m, 7H), 3.62 (m, 2H), 4.47 (m, 2H), 6.86 (m, 1H), 6.94 (m, 1H), 8.07 (m, 1H). MS APCI+ m/z 440 $[MH]^+$ |
| 58 | $R^3 = -CH_3$; $R^4 = -CH_3$; $R^6 = -(CH_2)_2OCH_2CH_3$; $R^{15} = -(CH_2)_2OH$ 1H -NMR (CD_3OD , 400MHz) δ : 1.08 (t, 3H), 2.40 (s, 3H), 3.30 (s, 6H), 3.62 (m, 4H), 3.81 (m, 2H), 3.92 (m, 2H), 4.84 (m, 2H), 6.96 (m, 1H), 8.18 (m, 1H), 8.40 (m, 1H). MS APCI+ m/z 429 $[MH]^+$ |
| 59 | $R^3 = -CH_2CH_3$; $R^4 = H$; $R^6 = -CH(CH_3)_2$; $R^{15} = -(CH_2)_2N(CH_3)_2$ 1H -NMR (CD_3OD , 400MHz) δ : 0.93 (d, 6H), 1.29 (t, 3H), 2.36 (s, 6H), 2.40 (s, 3H), 2.64 (m, 3H), 3.48 (m, 2H), 3.62 (m, 2H), 4.58 (m, 2H), 6.84 (m, 1H), 6.95 (m, 1H), 8.08 (m, 1H). MS APCI+ m/z 440 $[MH]^+$ |
| 60 | $R^3 = -CH_2CH_3$; $R^4 = H$; $R^6 = -(CH_2)_2OCH_2CH_3$; $R^{15} = -(CH_2)_2OCH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 1.30 (t, 3H), 2.42 (s, 3H), 3.40 (s, 3H), 3.50 (m, 2H), 3.60 (m, 4H), 3.68 (q, 2H), 4.64 (t, 2H), 4.80 (t, 2H), 6.95 (d, 1H), 8.15 (d, 1H), 8.45 (s, 1H). MS APCI+ m/z 443 $[MH]^+$ |

| | |
|----|---|
| 61 | $R^3 = -(\text{CH}_2)_2\text{OH}$; $R^4 = -\text{CH}_3$; $R^6 = -(\text{CH}_2)_2\text{OCH}_2\text{CH}_3$; $R^{15} = -\text{CH}_3$ $^1\text{H-NMR}$ (CD_3OD , 400MHz) δ : 1.11 (t, 3H), 2.40 (s, 3H), 3.03 (s, 3H), 3.37 (m, 3H), 3.61 (m, 2H), 3.85 (m, 4H), 3.93 (m, 2H), 4.80 (m, 2H), 6.94 (m, 1H), 8.16 (m, 1H), 8.32 (m, 1H). MS APCI+ m/z 429 $[\text{MH}]^+$ |
| 62 | $R^3 = -(\text{CH}_2)_2\text{OCH}_3$; $R^4 = \text{H}$; $R^6 = -(\text{CH}_2)_2\text{OCH}_2\text{CH}_3$; $R^{15} = -\text{CH}_3$ $^1\text{H-NMR}$ (CD_3OD , 400MHz) δ : 1.10 (3H, t), 2.42 (3H, s), 3.00 (3H, s), 3.40 (3H, s), 3.60 (2H, q), 3.65 (4H, m), 3.95 (2H, t), 4.80 (2H, t), 6.95 (1H, d), 8.15 (1H, d), 8.40 (1H, s). MS APCI+ m/z 429 $[\text{MH}]^+$ |
| 63 | $R^3 = -(\text{CH}_2)_2\text{OCH}_3$; $R^4 = -\text{CH}_3$; $R^6 = -(\text{CH}_2)_2\text{OCH}_2\text{CH}_3$; $R^{15} = -\text{CH}_3$ $^1\text{H-NMR}$ (CD_3OD , 400MHz) δ : 1.12 (t, 3H), 2.40 (s, 3H), 3.04 (s, 3H), 3.28(s, 3H), 3.36 (s, 3H), 3.61 (m, 2H), 3.67 (m, 2H), 3.91 (m, 4H), 4.60 (m, 2H), 6.93 (m, 1H), 8.15 (m, 1H), 8.28 (m, 1H). MS APCI+ m/z 443 $[\text{MH}]^+$ |
| 64 | $-\text{NR}^3\text{R}^4 =$  $;$ $R^6 = -\text{CH}(\text{CH}_3)_2$; $R^{15} = -\text{CH}_3$ $^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ : 1.00(m, 6H), 1.51(s, 9H), 2.41(m, 4H), 3.11(d, 3H), 3.57-3.87(m, 8H), 4.40-4.70(m, 2H), 6.91(m, 1H), 8.17(m, 1H), 8.36(m, 1H). MS APCI+ m/z 524 $[\text{MH}]^+$ |

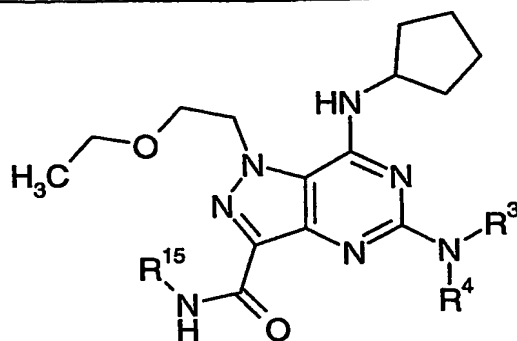
Example 56 – an 8M solution of methylamine in ethanol was used to provide the HNR^3R^4 amine

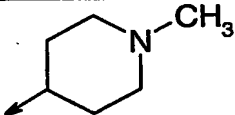
Example 657-(Cyclopentylamino)-5-(dimethylamino)-N-(2-(dimethylamino)ethyl)-1-(2-ethoxyethyl)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

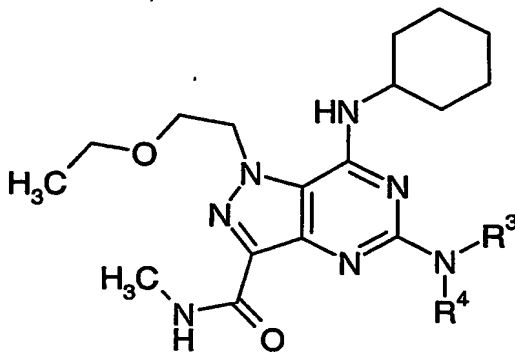
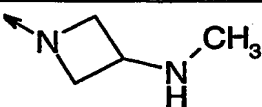
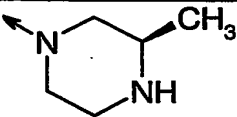
- 5 A solution of the amide of preparation 46 (55mg, 0.13mmol) and dimethylamine (5.6M solution in ethanol) (93 μ l, 0.52mmol) in dimethyl sulphoxide (2mL) was sealed in a ReactiVial™ and heated to 120°C overnight. The reaction mixture was diluted with dichloromethane (20mL) and washed with water (2 x 15mL) then brine (15mL). The organic layer was separated, dried over magnesium
- 10 sulphate and concentrated to give a colourless oil which crystallised on standing. The solid was purified by column chromatography on silica gel eluting with dichloromethane:methanol:0.88ammonia 97:3:0.25 to give a white solid.
- ¹H-NMR (CD₃OD, 400MHz) δ : 1.13 (t, 3H), 1.59 – 1.72 (m, 4H), 1.80 (m, 2H), 2.18 (m, 2H), 2.30 (s, 6H), 2.60 (t, 2H), 3.21 (s, 6H), 3.52 (m, 2H), 3.61 (t, 2H),
- 15 3.86 (t, 2H), 4.44 (m, 1H), 4.62 (t, 2H). MS APCI+ m/z 433 [MH]⁺

Examples 66-71

- The following compounds were prepared by a method similar to that described for example 65 using the appropriate HNR³R⁴ amine and the appropriate chloro
- 20 compound of preparations 46, 47, 48 and 49.



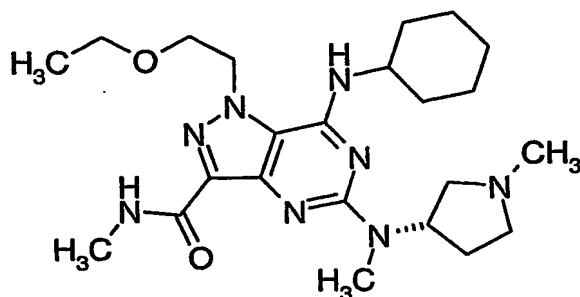
| Ex | |
|----|---|
| 66 | $R^3 = -CH_2CH_3$; $R^4 = H$; $R^{15} = -(CH_2)_2N(CH_3)_2$ 1H -NMR (CD_3OD , 400MHz) δ : 1.13 (t, 3H), 1.58 (m, 2H), 1.66 (m, 2H), 1.79 (m, 2H), 2.15 (m, 2H), 2.31 (s, 6H), 2.61 (t, 2H), 3.44 (m, 2H), 3.53 (m, 2H), 3.61 (t, 2H), 3.86 (t, 2H), 4.43 (m, 1H), 4.62 (t, 2H). MS APCI+ m/z 433 $[MH]^+$ |
| 67 | $R^3 = -CH_3$; $R^4 = -CH_3$; $R^{15} = -CH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.10 (t, 3H), 1.63 (m, 2H), 1.68 (m, 2H), 1.80 (m, 2H), 2.18 (m, 2H), 3.01 (s, 3H), 3.08 (s, 6H), 3.51 (m, 2H), 3.84 (t, 2H), 4.43 (m, 1H), 4.61 (t, 2H). MS APCI+ m/z 376 $[MH]^+$ |
| 68 | $R^3 = $  $; R^4 = -CH_3$; $R^{15} = -CH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.12 (t, 3H), 1.60 – 1.83 (complex, 10H), 1.89 (m, 2H), 2.18 (m, 4H), 2.35 (s, 3H), 3.02 (s, 3H), 3.05 (s, 3H), 3.51 (m, 2H), 3.85 (t, 2H), 4.39 (m, 1H), 4.61 (t, 2H), 4.69 (m, 1H). MS APCI+ m/z 459 $[MH]^+$ |
| 69 | $R^3 = -CH_3$; $R^4 = -CH_3$; $R^{15} = -(CH_2)_2OCH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.11 (t, 3H), 1.80 (m, 2H), 2.18 (m, 2H), 3.20 (s, 6H), 3.37 (s, 3H), 3.51 (m, 2H), 3.61 (m, 2H), 3.64 (m, 2H), 3.84 (t, 2H), 4.43 (m, 1H), 4.61 (t, 2H). MS APCI+ m/z 420 $[MH]^+$ |

| | |
|----|--|
| |  |
| 70 | <p>$-NR^3R^4 =$ </p> <p>1H-NMR (CD_3OD, 400MHz) δ: 1.13 (t, 3H), 1.21 – 1.50 (m, 5H), 1.69 (m, 1H), 1.82 (m, 2H), 2.12 (m, 2H), 2.37 (s, 3H), 3.01 (s, 3H), 3.53 (m, 2H), 3.63 (m, 1H), 3.85 (m, 4H), 4.08 (m, 1H), 4.26 (t, 2H), 4.63 (t, 2H). MS APCI+ m/z 431 $[MH]^+$</p> |
| 71 | <p>$-NR^3R^4 =$ </p> <p>1H-NMR (CD_3OD, 400MHz) δ: 1.15 (m, 6H), 1.24-1.53 (m, 5H), 1.73 (m, 1H), 1.84 (m, 2H), 2.16 (m, 2H), 2.60 (m, 1H), 2.80 (m, 2H), 2.95 (m, 1H), 3.04 (m, 6H), 3.56 (m, 2H), 3.86 (m, 2H), 4.03 (m, 1H), 4.61 (m, 4H). MS APCI+ m/z 445 $[MH]^+$</p> |

Examples 68 and 71 also added N-ethyldiisopropylamine (0.39mmol) to the dimethyl sulphoxide solution

Example 72

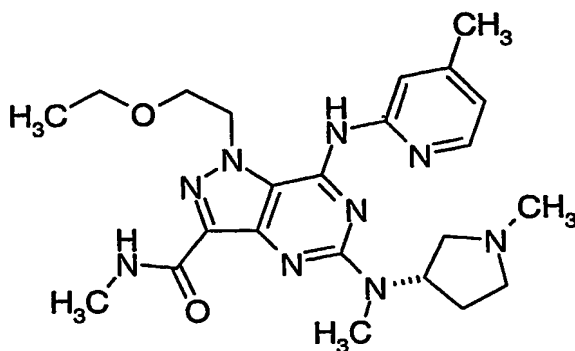
7-(Cyclohexylamino)-1-(2-ethoxyethyl)-N-methyl-5-[N-methyl-N-((3S)-1-methylpyrrolidin-3-yl)amino]-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide



- 5 The amide of preparation 49 (100mg, 0.26mmol), the amine of preparation 62 (246mg, 1.30mmol), N-ethyldiisopropylamine (450 μ L, 2.58mmol) and tetraethylammonium fluoride (39mg, 0.26mmol) were dissolved in 1-methyl-2-pyrrolidinone (1.5mL) and the reaction mixture stirred at 180°C for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue partitioned between
- 10 water and dichloromethane. The organic layer was dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:0.88ammonia 98:2:0.25 to yield the title product as a white solid, 15mg.
- 15 ¹H-NMR (CD₃OD, 400MHz) δ : 1.11 (t, 3H), 1.22-1.32 (m, 5H), 1.75 (m, 3H), 2.13 (m, 4H), 2.40 (s, 3H), 2.57-2.91 (m, 4H), 3.05 (m, 6H), 3.56 (m, 2H), 3.83 (m, 2H), 4.04 (m, 1H), 4.60 (m, 2H), 5.56 (m, 1H). MS APCI+ m/z 459 [MH]⁺

Example 73

20 1-(2-Ethoxyethyl)-N-methyl-5-[N-methyl-N-((3S)-1-methylpyrrolidin-3-yl)amino]-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

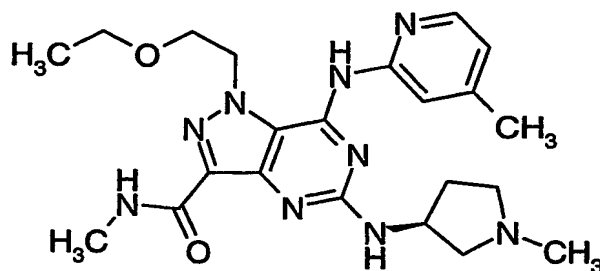


The title compound was prepared by a method similar to that described for example 72 using the amide of preparation 39 and the amine of preparation 63.

¹H-NMR (CD₃OD, 400MHz) δ: 1.11(t, 3H), 1.90-2.90(m, 12H), 3.05(s, 3H), 3.18(s, 3H), 3.60(q, 2H), 3.93(t, 2H), 4.79(t, 2H), 5.54(m, 1H), 6.96(d, 1H), 8.17(d, 1H), 8.24(m, 1H). MS APCI+ m/z 468 [MH]⁺

Example 74

1-(2-Ethoxyethyl)-N-methyl-5-((3S)-3-(1-methylpyrrolidin-3-yl)amino-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

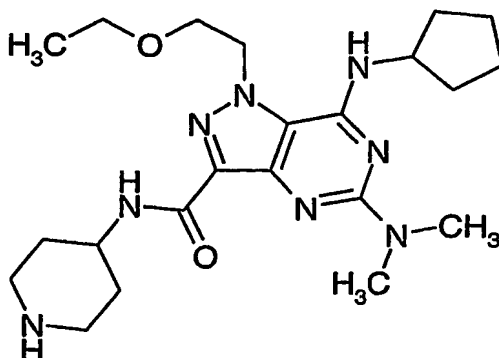


The title compound was prepared by a method similar to that described for example 72 using the amide of preparation 39 and the amine of preparation 65.

¹H-NMR (CD₃OD, 400MHz) δ: 1.08 (t, 3H), 1.96 (m, 1H), 2.29 (m, 1H), 2.40 (s, 3H), 2.47 (s, 3H), 3.04 (s, 3H), 3.44 (m, 2H), 3.62 (m, 3H), 3.79 (m, 1H), 3.89 (m, 3H), 4.77 (m, 2H), 6.93 (m, 1H), 8.14 (m, 1H), 8.44 (m, 1H). MS APCI+ m/z 454 [MH]⁺

Example 75

7-(Cyclopentylamino)-5-(dimethylamino)-1-(2-ethoxyethyl)-N-(piperidin-4-yl)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

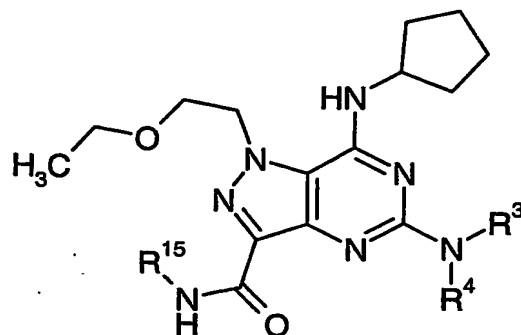


A solution of the amide of preparation 45 (60mg, 0.11mmol) and dimethylamine (5.6M in ethanol) (80.4μL, 0.45mmol) in dimethyl sulfoxide (2mL) was heated in a sealed ReactiVial™ at 120°C for 4 hours. The reaction mixture was diluted with dichloromethane and washed with water (x2) and brine (x2). The organics were dried over magnesium sulphate and concentrated *in vacuo* to give a yellow oil, which was redissolved in dichloromethane (2mL) and trifluoroacetic acid (2mL) before being stirred at room temperature for 2hours. The reaction was concentrated *in vacuo*, re-dissolved in dichloromethane, washed with sodium carbonate solution, brine and then dried over magnesium sulphate. The solvent was removed *in vacuo* and the resulting oil purified by column chromatography on silica gel eluting with dichloromethane:methanol 98:2 to 95:5 to 90:10:1 to yield the title product.

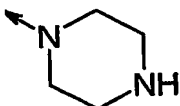
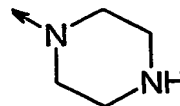
¹H-NMR (CD₃OD 400MHz) δ: 1.13 (t, 3H), 1.64 (m, 6H), 1.79 (m, 2H), 2.16 (m, 4H), 2.87 (t, 2H), 3.19 (s, 8H), 3.53 (m, 2H), 3.86 (t, 2H), 4.10 (m, 1H), 4.44 (m, 1H), 4.63 (t, 2H). MS APCI+ m/z 445 [MH]⁺.

Examples 76-82

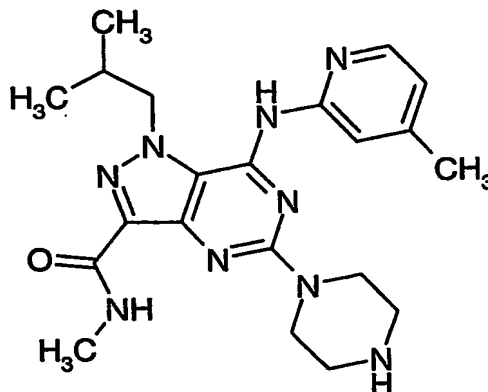
The following compounds were prepared by a method similar to that described for example 75 using the appropriate HNR³R⁴ amine and the appropriate chloro compound from preparations 44, 45, 47 and 48.



| Ex | |
|----|---|
| 76 | <p>$R^3 = -CH_2CH_3$; $R^4 = H$; $R^{15} =$ </p> <p>1H-NMR (CD_3OD 400MHz) δ: 1.13 (t, 3H), 1.25 (t, 3H), 1.54 -1.71 (m, 6H), 1.79 (m, 2H), 2.05 (m, 2H), 2.15 (m, 2H), 2.76 (t, 2H), 3.09 (m, 2H), 3.40 (m, 2H), 3.53 (m, 2H), 3.86 (t, 2H), 4.07 (m, 1H), 4.42 (m, 1H), 4.62 (t, 2H). MS APCI+ m/z 445 $[MH]^+$</p> |
| 77 | <p>$R^3 = -CH_3$; $R^4 = -CH_3$; $R^{15} = -(CH_2)_2NH_2$</p> <p>1H-NMR (CD_3OD, 400MHz) δ: 1.12 (t, 3H), 1.58 – 1.73 (m, 4H), 1.79 (m, 2H), 2.19 (m, 2H), 3.10 (t, 2H), 3.20 (s, 6H), 3.52 (m, 2H), 3.69 (t, 2H), 3.85 (t, 2H), 4.44 (m, 1H), 4.63 (t, 2H). MS APCI+ m/z 405 $[MH]^+$</p> |
| 78 | <p>$R^3 = -CH_2CH_3$; $R^4 = H$; $R^{15} = -(CH_2)_2NH_2$</p> <p>1H-NMR (CD_3OD, 400MHz) δ: 1.13 (t, 3H), 1.23 (t, 3H), 1.55 – 1.71 (m, 4H), 1.80 (m, 2H), 2.15 (m, 2H), 2.93 (t, 2H), 3.42 (m, 2H), 3.53 (m, 2H), 3.58 (t, 2H), 3.86 (t, 2H), 4.43 (m, 1H), 4.62 (t, 2H). MS APCI+ m/z 405 $[MH]^+$</p> |
| 79 | <p>$R^3 = -CH(CH_3)_2$; $R^4 = -CH_3$; $R^{15} = -(CH_2)_2NH_2$</p> <p>1H-NMR (CD_3OD, 400MHz) δ: 1.13 (t, 3H), 1.21 (d, 6H), 1.58 – 1.72 (m, 4H), 1.80 (m, 2H), 2.18 (m, 2H), 2.90 (t, 2H), 3.02 (s, 3H), 3.49 – 3.60 (m, 4H), 3.86 (t, 2H), 4.42 (m, 1H), 4.63 (t, 2H), 5.11 (m, 1H). MS APCI+ m/z 433 $[MH]^+$</p> |

| | |
|----|---|
| 80 | $R^3 = -CH_2CH_3$; $R^4 = -CH_2CH_3$; $R^{15} = -(CH_2)_2NH_2$ 1H -NMR (CD_3OD , 400MHz) δ : 1.14 (t, 3H), 1.23 (t, 6H), 1.59 – 1.72 (m, 4H), 1.80 (m, 2H), 2.17 (m, 2H), 2.89 (t, 2H), 3.50 – 3.57 (m, 4H), 3.66 (m, 4H), 3.86 (t, 2H), 4.42 (m, 1H), 4.63 (t, 2H). MS APCI+ m/z 433 $[MH]^+$ |
| 81 | $-NR^3R^4 = $  $; R^{15} = -CH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.12 (t, 3H), 1.60 (m, 2H), 1.68 (m, 2H), 1.82 (m, 2H), 2.17 (m, 2H), 2.92 (m, 4H), 3.01 (s, 3H), 3.52 (m, 2H), 3.84 (m, 4H), 3.88 (m, 2H), 4.40 (m, 1H), 4.61 (m, 2H). MS APCI+ m/z 417 $[MH]^+$ |
| 82 | $-NR^3R^4 = $  $; R^{15} = -(CH_2)_2OCH_3$ 1H -NMR (CD_3OD , 400MHz) δ : 1.12 (t, 3H), 1.63 (m, 2H), 1.70 (m, 2H), 1.80 (m, 2H), 2.17 (m, 2H), 2.90 (m, 4H), 3.40 (s, 3H), 3.51 (m, 2H), 3.61 (m, 2H), 3.63 (m, 2H), 3.83 (m, 6H), 4.41 (m, 1H), 4.63 (t, 2H). MS APCI+ m/z 461 $[MH]^+$ |

- Examples 81 and 82 used *tert*-butyl piperazine-1-carboxylate as the HNR^3R^4 amine

Example 831-Isobutyl-N-methyl-7-(4-methylpyridin-2-ylamino)-5-(piperazin-1-yl)-1H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

5 The compound of example 64 (20mg, 0.04mmol) was dissolved in a mixture of trifluoroacetic acid (500μL) and dichloromethane (5mL) and the reaction mixture stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (10mL) and 2M sodium carbonate solution (10mL). The aqueous was extracted with ethyl
 10 acetate (10mL), the organics were combined, dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonia 95:5:0 to 95:5:0.5 to yield the title product, 10mg.

¹H-NMR (CD₃OD, 400MHz) δ: 0.92(d, 6H), 2.29(m, 1H), 2.40(s, 3H), 2.95(m,
 15 4H), 3.04(s, 3H), 3.81(m, 4H), 4.51(m, 2H), 6.97(m, 1H), 7.38(m, 1H), 8.16(d, 1H). MS APCI+ m/z 424 [MH]⁺

Assay

The compounds of the invention are inhibitors of cyclic guanylate
 20 monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE-5 inhibitors). Preferred compounds suitable for use in accordance with the present invention are potent and selective PDE5 inhibitors. *In vitro* PDE inhibitory activities against cyclic guanosine 3',5'-monophosphate (cGMP) and cyclic adenosine 3',5'-monophosphate (cAMP) phosphodiesterases can be determined by
 25 measurement of their IC₅₀ values (the concentration of compound required for 50% inhibition of enzyme activity).

The required PDE enzymes can be isolated from a variety of sources, including human corpus cavernosum, human and rabbit platelets, human cardiac ventricle, human skeletal muscle and bovine retina, essentially by a modification of the method of Thompson, WJ *et al.*; Biochemistry 18(23), 5228-5237, 1979, as described by Ballard SA *et al.*; J. Urology 159(6), 2164-2171, 1998. In particular, cGMP-specific PDE5 and cGMP-inhibited cAMP PDE3 can be obtained from human corpus cavernosum tissue, human platelets or rabbit platelets; cGMP-stimulated PDE2 was obtained from human corpus cavernosum; calcium/calmodulin (Ca/CAM)-dependent PDE1 from human cardiac ventricle; cAMP-specific PDE4 from human skeletal muscle; and photoreceptor PDE6 from bovine retina. Phosphodiesterases 7-11 can be generated from full length human recombinant clones transfected into SF9 cells.

Assays can be performed either using a modification of the "batch" method of Thompson WJ and Appleman MM; Biochemistry 10(2), 311-316, 1971, essentially as described by Ballard SA *et al.*; J. Urology 159(6), 2164-2171, 1998, or using a scintillation proximity assay for the direct detection of [³H]-labelled AMP/GMP using a modification of the protocol described by Amersham plc under product code TRKQ7090/7100. In summary, for the scintillation proximity assay the effect of PDE inhibitors was investigated by assaying a fixed amount of enzyme in the presence of varying inhibitor concentrations and low substrate, (cGMP or cAMP in a 3:1 ratio unlabelled to [³H]-labeled at a concentration of $\sim 1/3 K_m$ or less) such that $IC_{50} \cong K_i$. The final assay volume was made up to 100 μ l with assay buffer [20mM Tris-HCl pH 7.4, 5mM MgCl₂, 1mg/ml bovine serum albumin]. Reactions were initiated with enzyme, incubated for 30-60min at 30°C to give <30% substrate turnover and terminated with 50 μ l yttrium silicate SPA beads (containing 3mM of the respective unlabelled cyclic nucleotide for PDEs 9 and 11). Plates were re-sealed and shaken for 20min, after which the beads were allowed to settle for 30min in the dark and then counted on a TopCount plate reader (Packard, Meriden, CT) Radioactivity units were converted to % activity of an uninhibited control (100%), plotted against

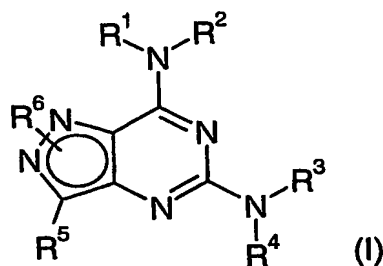
inhibitor concentration and inhibitor IC_{50} values obtained using the 'Fit Curve' Microsoft Excel extension.

5 All compounds of the invention have an activity against PDE-5 of less than 10,000nM. IC_{50} values for representative preferred compounds are listed in the table below.

| Example | IC_{50} (nM) | Example | IC_{50} (nM) |
|---------|----------------|---------|----------------|
| 8 | 0.33 | 32 | 0.73 |
| 14 | 0.26 | 50 | 1.31 |
| 16 | 0.40 | 56 | 1.63 |
| 17 | 0.24 | 58 | 0.13 |
| 18 | 0.06 | 60 | 0.57 |
| 19 | 0.09 | 61 | 0.12 |
| 22 | 0.02 | 62 | 1.88 |
| 23 | 0.04 | 71 | 2.95 |
| 29 | 0.50 | 73 | 0.42 |
| 30 | 1.65 | | |

Claims

1. A compound of formula (I)



wherein

R^1 is a cyclic group selected from R^A , R^B , R^C and R^D , each of which is optionally substituted with one or more R^7 groups;

R^{2a} is hydrogen or C_1 - C_2 alkyl;

R^3 and R^4 are each independently C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl or C_3 - C_{10} cycloalkyl, each of which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups, or hydrogen;

or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

R^5 is $-Y-CONR^{15}R^{16}$;

R^6 , which may be attached at N^1 or N^2 , is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl, each of which is optionally substituted by C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy or a cyclic group selected from R^J , R^K , R^L and R^M , or R^6 is R^N , C_3 - C_7 cycloalkyl or C_3 - C_7 halocycloalkyl, each of which is optionally substituted by C_1 - C_6 alkoxy or C_1 - C_6 haloalkoxy, or R^6 is hydrogen;

R^7 is halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$ or CN;

R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{12} , $CONR^{12}R^{13}$, CN , R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

R^9 is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or CO_2R^{12} ;

R^{10} is halo, C_3 - C_{10} cycloalkyl, C_3 - C_{10} halocycloalkyl, phenyl, OR^{12} , $OC(O)R^{12}$, NO_2 , $NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}CO_2R^{14}$, $C(O)R^{12}$, CO_2R^{13} , $CONR^{12}R^{13}$, CN , oxo, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, the last two of which are optionally substituted by R^{11} ;

R^{11} is phenyl, $NR^{12}R^{13}$ or $NR^{12}CO_2R^{14}$;

R^{12} and R^{13} are each independently hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^{14} is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^{15} and R^{16} are each independently selected from
hydrogen,

C_1 - C_6 haloalkyl,

C_1 - C_6 alkyl optionally substituted with

R^{17} ,

$-NR^{18}R^{19}$,

$-CO_2R^{20}$,

$-CONR^{21}R^{22}$,

R^{23} or

phenyl optionally substituted by

halo,

C_1 - C_6 alkyl or

R^{17} ,

C_3 - C_7 cycloalkyl optionally substituted with

C_1 - C_6 alkyl,

R^{17} or

$-NR^{18}R^{19}$, and

R^{23} ;

or $NR^{15}R^{16}$ constitutes a 3- to 8-membered ring which may optionally include one or more further heteroatoms selected from nitrogen, oxygen and sulphur, and which may optionally be further substituted with R^{17} , C_1 - C_6 haloalkyl, $-CO_2R^{20}$, $-CONR^{21}R^{22}$, oxo or C_1 - C_6 alkyl optionally substituted by R^{17} ;

R^{17} is hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 (haloalkyl)oxy or C_3 - C_7 cycloalkyloxy;

R^{18} and R^{19} are each independently selected from hydrogen and C_1 - C_6 alkyl;

or $-NR^{18}R^{19}$ constitutes an azetidine, pyrrolidine, piperidine or morpholine ring;

R^{20} is hydrogen or C_1 - C_6 alkyl;

R^{21} and R^{22} are each independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl and C_3 - C_7 cycloalkyl;

or $-NR^{21}R^{22}$ constitutes a 3- to 8-membered ring which may optionally include one or more further heteroatoms selected from nitrogen, oxygen and sulphur;

R^{23} is a saturated 3- to 8-membered ring which includes at least one heteroatom selected from nitrogen, oxygen and sulphur, which ring may optionally be substituted by one or more C_1 - C_6 alkyl groups, provided that the group R^{23} is joined to the parent molecule by a covalent bond to a carbon atom of said ring;

R^A and R^J are each independently a C_3 - C_{10} cycloalkyl or C_3 - C_{10} cycloalkenyl group, each of which may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic and which may be fused to either

(a) a monocyclic aromatic ring selected from a benzene ring and a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, or

(b) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;

R^B and R^K are each independently a phenyl or naphthyl group, each of which may be fused to

- (a) a C_5 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl ring,
- (b) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, or
- (c) a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;

R^C , R^L and R^N are each independently a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated or partly unsaturated ring system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, which ring may be fused to a C_5 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl group or a monocyclic aromatic ring selected from a benzene ring and a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;

R^D and R^M are each independently a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur, which ring may further be fused to

- (a) a second 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur;
- (b) C_5 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl ring;
- (c) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur; or
- (d) a benzene ring;

R^E , R^F and R^G are each independently a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^H is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur; and

Y is a covalent bond, C_1 - C_6 alkylene or C_3 - C_7 cycloalkylene;

a tautomer thereof or a pharmaceutically acceptable salt, solvate or polymorph of said compound or tautomer.

2. A compound according to claim 1 wherein R^1 is R^A , which is optionally substituted with one or more R^7 groups; and
 R^A is a C_3 - C_{10} cycloalkyl group, which may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic, which may be fused to either
 - (a) a monocyclic aromatic ring selected from a benzene ring and a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, or
 - (b) a 5-, 6- or 7-membered heteroalicyclic ring containing up to three heteroatoms selected from nitrogen, oxygen and sulphur.
3. A compound according to claim 2 wherein R^A is a monocyclic C_3 - C_8 cycloalkyl group.
4. A compound according to claim 3 wherein R^A is a monocyclic C_5 - C_7 cycloalkyl group.
5. A compound according to claim 4 wherein R^A is cyclopentyl or cyclohexyl.
6. A compound according to claim 1 wherein R^1 is R^B , which is optionally substituted with one or more R^7 groups.
7. A compound according to claim 6 wherein R^B is phenyl.

8. A compound according to claim 1 wherein R^1 is R^C , which is optionally substituted with one or more R^7 groups.
9. A compound according to claim 8 wherein R^C is a monocyclic saturated or partly unsaturated ring system containing between 3 and 8 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.
10. A compound according to claim 9 wherein R^C is a monocyclic saturated or partly unsaturated ring system containing between 5 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.
11. A compound according to claim 10 wherein R^C is a monocyclic saturated ring system containing between 5 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.
12. A compound according to claim 1 wherein R^1 is R^D , which is optionally substituted with one or more R^7 groups.
13. A compound according to claim 12 wherein R^D is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur.
14. A compound according to claim 13 wherein R^D is a 5-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur and optionally up to two further nitrogen atoms in the ring, or a 6-membered heteroaromatic ring including 1, 2 or 3 nitrogen atoms.
15. A compound according to claim 14 wherein R^D is furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl.
16. A compound according to claim 15 wherein R^D is pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl.

17. A compound according to any one of claims 1 to 16 wherein R^7 is halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, OR^{12} or $CONR^{12}R^{13}$.
18. A compound according to claim 17 wherein R^7 is halo, C_1-C_3 alkyl, C_1-C_3 alkoxy, hydroxy or $CONH(C_1-C_3 \text{ alkyl})$.
19. A compound according to claim 18 wherein R^7 is fluoro, methyl, ethyl, hydroxy, methoxy, propoxy or $CONHMe$.
20. A compound according to any one of claims 1 to 19 wherein R^2 is hydrogen or methyl.
21. A compound according to claim 20 wherein R^2 is hydrogen.
22. A compound according to any one of claims 1 to 21 wherein R^3 is hydrogen, C_1-C_6 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups; and wherein R^E is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.
23. A compound according to claim 22 wherein R^3 is hydrogen, C_1-C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups; and wherein R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.
24. A compound according to claim 23 wherein R^3 is R^E , which is optionally substituted with one or more R^9 groups and wherein R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms containing one nitrogen atom.

25. A compound according to claim 24 wherein R^E is azetidiny, pyrrolidinyl or piperidinyl.
26. A compound according to claim 23 wherein R^3 is C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups and wherein R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $NR^{12}R^{13}$, $NR^{12}CO_2R^{14}$, CO_2R^{12} , $CONR^{12}R^{13}$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups.
27. A compound according to claim 26 wherein R^8 is hydroxy, methoxy, methoxyphenyl, NH_2 , $NHMe$, NMe_2 , $NHCO_2^tBu$, $NMeCO_2^tBu$, CO_2H , $CONHMe$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups.
28. A compound according to claim 27 wherein R^8 is R^G , which is optionally substituted with one or more R^9 groups and wherein R^G is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur.
29. A compound according to claim 28 wherein R^G is a monocyclic saturated ring system containing between 3 and 7 ring atoms containing one nitrogen atom and optionally one oxygen atom.
30. A compound according to claim 29 wherein R^G is pyrrolidinyl, piperidinyl or morpholinyl.
31. A compound according to claim 27 wherein R^8 is R^H , which is optionally substituted with one or more R^9 groups and wherein R^H is a 5- or 6-membered heteroaromatic ring containing up to two nitrogen atoms.
32. A compound according to claim 31 wherein R^H is pyrazolyl.
33. A compound according to any one of claims 22 to 32 wherein R^9 is methyl or CO_2^tBu .

34. A compound according to claim 23 wherein R^3 is hydrogen or C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^3 is azetidiny, pyrrolidiny or piperidiny, each of which is optionally substituted with one or more R^9 groups, wherein R^8 is hydroxy, methoxy, methoxyphenyl, NH_2 , $NHMe$, NMe_2 , $NHCO_2^tBu$, $NMeCO_2^tBu$, CO_2H , $CONHMe$, pyrrolidiny, piperidiny, morpholinyl or pyrazolyl, the last four of which are optionally substituted with one or more R^9 groups and wherein R^9 is methyl or CO_2^tBu .

35. A compound according to any one of claims 1 to 34 wherein R^4 is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl.

36. A compound according to claim 35 wherein R^4 is hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl.

37. A compound according to claim 36 wherein R^4 is hydrogen, methyl or ethyl.

38. A compound according to any one of claims 1 to 21 wherein $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups and wherein R^F is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms containing at least one nitrogen atom and optionally one other atom selected from oxygen and sulphur.

39. A compound according to claim 38 wherein R^F is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms containing one or two nitrogen atoms and optionally one other atom selected from oxygen and sulphur.

40. A compound according to claim 39 wherein R^F is selected from azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholinyl, 3-azabicyclo[3.1.0]hex-3-yl, homopiperaziny, 2,5-diazabicyclo[4.3.0]non-2-yl, 3,8-diazabicyclo[3.2.1]oct-3-yl, 3,8-diazabicyclo[3.2.1]oct-8-yl, 1,4-diazabicyclo[4.3.0]non-4-yl and 1,4-diazabicyclo[3.2.2]non-4-yl.

41. A compound according to any one of claims 38 to 40 wherein R^{10} is halo, OR^{12} , $NR^{12}R^{13}$, $NR^{12}CO_2R^{14}$, CO_2R^{13} , oxo, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, the last two of which are optionally substituted by R^{11} .

42. A compound according to claim 41 wherein R^{10} is halo, methyl, ethyl, isopropyl, hydroxy, methoxy, NH_2 , $NHMe$, NMe_2 , $NHCO_2^tBu$, CO_2H , CO_2^tBu , oxo, benzyl, $-CH_2NH_2$, $-CH_2NHMe$, CH_2NMe_2 or $-CH_2NMeCO_2^tBu$.

43. A compound according to any one of claims 1 to 42 wherein Y is a covalent bond.

44. A compound according to any one of claims 1 to 43 wherein

R^{15} and R^{16} are each independently selected from hydrogen, C_1 - C_6 alkyl optionally substituted with R^{17} , $-NR^{18}R^{19}$, $-CO_2R^{20}$, $-CONR^{21}R^{22}$, R^{23} or phenyl optionally substituted by halo, C_1 - C_6 alkyl or R^{17} , C_3 - C_7 cycloalkyl and R^{23} , or $NR^{15}R^{16}$ constitutes a 5- to 7-membered ring which may optionally include one or more further heteroatoms selected from nitrogen and oxygen, and which may optionally be further substituted with R^{17} , $-CO_2R^{20}$, $-CONR^{21}R^{22}$ or C_1 - C_6 alkyl optionally substituted by R^{17} ;

R^{17} is hydroxy, C_1 - C_6 alkoxy or C_3 - C_7 cycloalkyloxy;

R^{21} and R^{22} are each independently selected from hydrogen, C_1 - C_6 alkyl, and C_3 - C_7 cycloalkyl, or $-NR^{21}R^{22}$ constitutes a 5- to 8-membered ring which may optionally include one or more further heteroatoms selected from nitrogen and oxygen; and

R^{23} is a saturated 5- to 7-membered ring which includes at least one heteroatom selected from nitrogen and oxygen, which ring may optionally be substituted by one or more C_1 - C_6 alkyl groups.

45. A compound according to claim 44 wherein R^{15} and R^{16} are each independently selected from hydrogen and C_1 - C_6 alkyl optionally substituted with R^{17} or $-NR^{18}R^{19}$.

46. A compound according to any one of claims 1 to 45 wherein R^6 is positioned on N^1 .

47. A compound according to any one of claims 1 to 46 wherein R^6 is C_1 - C_6 alkyl or C_1 - C_6 haloalkyl, each of which is optionally substituted by C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy or a cyclic group selected from R^J , R^L and R^M , or R^6 is R^N or hydrogen;
 R^J is a C_3 - C_7 monocyclic cycloalkyl group;
 R^L and R^N are each independently a monocyclic, saturated or partly unsaturated ring system containing between 4 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur; and
 R^M is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur.

48. A compound according to claim 47 wherein R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy or a cyclic group selected from R^J , R^L and R^M , or R^6 is R^N or hydrogen;
 R^J is cyclopropyl or cyclobutyl;
 R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur; and
 R^M is a 5- or 6-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur.

49. A compound according to claim 48 wherein R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy or a cyclic group selected from R^J , R^L and R^M , or R^6 is R^N or hydrogen;
 R^J is cyclopropyl or cyclobutyl;
 R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms containing one heteroatom selected from nitrogen, oxygen and sulphur; and
 R^M is a 5- or 6-membered heteroaromatic ring containing one nitrogen atom.

50. A compound according to claim 49 wherein R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy, cyclopropyl, cyclobutyl, tetrahydrofuranyl, tetrahydropyranyl or pyridinyl, or R^6 is hydrogen or tetrahydropyranyl.

51. A compound according to claim 50 wherein R^6 is hydrogen, methyl, ethyl, isopropyl, isobutyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, propoxyethyl, 2,2,2-trifluoroethyl, tetrahydrofuranylmethyl, tetrahydropyranylmethyl, tetrahydropyranyl or pyridinylmethyl.

52. A compound according to claim 1 wherein

R^3 is hydrogen, C_1 - C_4 alkyl, which is optionally substituted with one or more R^8 groups, or R^E , which is optionally substituted with one or more R^9 groups;

R^4 is hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

or $-NR^3R^4$ forms R^F , which is optionally substituted with one or more R^{10} groups;

R^6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl, each of which is optionally substituted by C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy or a cyclic group selected from R^J , R^L and R^M , or R^6 is R^N or hydrogen;

R^A is a monocyclic C_3 - C_8 cycloalkyl group;

R^B is phenyl;

R^C is a monocyclic saturated or partly unsaturated ring system containing between 3 and 8 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^D is a 5- or 6-membered heteroaromatic ring containing up to three heteroatoms independently selected from nitrogen, oxygen and sulphur;

R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^F is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^J is cyclopropyl or cyclobutyl;

R^L and R^N are each independently a monocyclic saturated ring system containing either 5 or 6 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^M is a 5- or 6-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur; and

Y is a covalent bond.

53. A compound according to claim 52 wherein R^1 is a cyclic group selected from R^A , R^B , R^C and R^D , each of which is optionally substituted with one or more R^7 groups;

R^7 is halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, OR^{12} or $CONR^{12}R^{13}$;

R^8 is halo, phenyl, C_1 - C_6 alkoxyphenyl, OR^{12} , $NR^{12}R^{13}$, $NR^{12}CO_2R^{14}$, CO_2R^{12} , $CONR^{12}R^{13}$, R^G or R^H , the last two of which are optionally substituted with one or more R^9 groups;

R^A is a monocyclic C_5 - C_7 cycloalkyl group;

R^B is phenyl;

R^C is a monocyclic saturated ring system containing between 5 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur;

R^D is a 5-membered heteroaromatic ring containing a heteroatom selected from nitrogen, oxygen and sulphur and optionally up to two further nitrogen atoms in the ring, or a 6-membered heteroaromatic ring including 1, 2 or 3 nitrogen atoms;

R^E is a monocyclic saturated ring system containing between 3 and 7 ring atoms containing one nitrogen atom;

R^F is a monocyclic or, when there are an appropriate number of ring atoms, polycyclic saturated ring system containing between 3 and 10 ring atoms containing at least one nitrogen atom and optionally one other atom selected from oxygen and sulphur;

R^G is a monocyclic saturated ring system containing between 3 and 7 ring atoms, of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur; and

R^H is a 5- or 6-membered heteroaromatic ring containing up to two nitrogen atoms.

54. A compound according to claim 1 selected from:

1-(2-ethoxyethyl)-*N*-ethyl-5-(ethylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

5-(dimethylamino)-1-(2-ethoxyethyl)-*N*-methyl-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

5-(dimethylamino)-1-(2-ethoxyethyl)-*N*-(2-(methylamino)ethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

5-(dimethylamino)-*N*-(2-(dimethylamino)ethyl)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

5-(dimethylamino)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-*N*-(piperidin-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

5-(dimethylamino)-1-(2-ethoxyethyl)-*N*-(2-methoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

(2*R*)-2-[[5-(dimethylamino)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]amino}propionic acid,

3-[[5-(dimethylamino)-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbonyl]amino}propionic acid,

1-(2-ethoxyethyl)-*N*-methyl-7-(4-methylpyridin-2-ylamino)-5-(piperazin-1-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

1-(2-ethoxyethyl)-*N*-methyl-5-((3*R*)-3-methylpiperazin-1-yl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

1-(2-ethoxyethyl)-*N*-ethyl-5-((3*R*)-3-methylpiperazin-1-yl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

1-(2-ethoxyethyl)-5-(ethylamino)-*N*-methyl-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

1-(2-ethoxyethyl)-*N*-(2-methoxyethyl)-5-(methylamino)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

5-(dimethylamino)-1-(2-ethoxyethyl)-*N*-(2-hydroxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

1-(2-ethoxyethyl)-5-(ethylamino)-*N*-(2-methoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

1-(2-ethoxyethyl)-5-(*N*-(2-hydroxyethyl)-*N*-methylamino)-*N*-methyl-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

1-(2-ethoxyethyl)-5-((2-methoxyethyl)amino)-*N*-methyl-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide,

7-(cyclohexylamino)-1-(2-ethoxyethyl)-*N*-methyl-5-((3*R*)-3-methylpiperazin-1-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide, and

1-(2-ethoxyethyl)-*N*-methyl-5-[*N*-methyl-*N*-((3*S*)-1-methylpyrrolidin-3-yl)amino]-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxamide

and tautomers thereof and pharmaceutically acceptable salts, solvates and polymorphs of said compound or tautomer.

55. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of claims 1 to 54, or pharmaceutically acceptable salts, solvates or polymorphs thereof, and a pharmaceutically acceptable diluent or carrier.

56. A compound of formula (I) as claimed in any one of claims 1 to 54, or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use as a medicament.

57. A compound of formula (I) as claimed in any one of claims 1 to 54, or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use in accordance with claim 56 as a medicament for the treatment of a disease or condition where inhibition of PDE5 is known, or can be shown, to produce a beneficial effect.

58. A compound of formula (I) as claimed in any one of claims 1 to 54, or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use in accordance with claim 56 or 57 as a medicament for the treatment of a disease or condition selected from hypertension (including essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension), congestive heart failure, angina (including stable, unstable and variant (Prinzmetal) angina), stroke, coronary artery disease, congestive heart failure,

conditions of reduced blood vessel patency (such as post-percutaneous coronary angioplasty), peripheral vascular disease, atherosclerosis, nitrate-induced tolerance, nitrate tolerance, diabetes, impaired glucose tolerance, metabolic syndrome, obesity, sexual dysfunction (including male erectile disorder, impotence, female sexual arousal disorder, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual pain disorder, female sexual orgasmic dysfunction and sexual dysfunction due to spinal cord injury), premature labour, pre-eclampsia, dysmenorrhea, polycystic ovary syndrome, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, chronic obstructive pulmonary disease, acute respiratory failure, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, gut motility disorders (including irritable bowel syndrome), Kawasaki's syndrome, multiple sclerosis, Alzheimer's disease, psoriasis, skin necrosis, scarring, fibrosis, pain (particularly neuropathic pain), cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and haemorrhoids.

59. A method of treatment of a disease or condition where inhibition of PDE5 is known, or can be shown, to produce a beneficial effect, in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of formula (I) as claimed in any one of claims 1 to 54, or a pharmaceutically acceptable salt, solvate or polymorph thereof.

60. Use of a compound of formula (I) as claimed in any one of claims 1 to 54, or a pharmaceutically acceptable salt, solvate or polymorph thereof, in the preparation of a medicament for the treatment of a disease or condition where inhibition of PDE5 is known, or can be shown, to produce a beneficial effect.

61. Use according to either claim 59 or claim 60, wherein the disease or condition is selected from hypertension (including essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension), congestive heart failure, angina (including stable, unstable and variant (Prinzmetal) angina), stroke, coronary artery disease, congestive heart failure, conditions of reduced blood vessel patency (such as post-percutaneous coronary angioplasty), peripheral vascular disease, atherosclerosis, nitrate-induced tolerance,

nitrate tolerance, diabetes, impaired glucose tolerance, metabolic syndrome, obesity, sexual dysfunction (including male erectile disorder, impotence, female sexual arousal disorder, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual pain disorder, female sexual orgasmic dysfunction and sexual dysfunction due to spinal cord injury), premature labour, pre-eclampsia, dysmenorrhea, polycystic ovary syndrome, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, chronic obstructive pulmonary disease, acute respiratory failure, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, gut motility disorders (including irritable bowel syndrome), Kawasaki's syndrome, multiple sclerosis, Alzheimer's disease, psoriasis, skin necrosis, scarring, fibrosis, pain (particularly neuropathic pain), cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and haemorrhoids.

62. Use according to claim 61 wherein the disease or condition is hypertension.

63. Use according to claim 62 wherein the disease or condition is selected from essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension.

64. Use according to claim 61 wherein the disease or condition is diabetes.

65. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of claims 1 to 54, or pharmaceutically acceptable salts, solvates or polymorphs thereof, and a second pharmaceutically active agent selected from aspirin, angiotensin II receptor antagonists (such as losartan, candesartan, telmisartan, valsartan, irbesartan and eprosartan), calcium channel blockers (such as amlodipine), beta-blockers (i.e. beta-adrenergic receptor antagonists such as sotalol, propranolol, timolol, atenolol, carvedilol and metoprolol), C11027, CCR5 receptor antagonists, imidazolines, sGCa's (soluble guanylate cyclase activators) antihypertensive agents, diuretics (such as hydrochlorothiazide, torsemide, chlorothiazide, chlorthalidone and amiloride), alpha adrenergic antagonists (such as doxazosin), ACE (angiotensin converting enzyme) inhibitors (such as quinapril, enalapril, ramipril and lisinopril), aldosterone receptor antagonists (such as eplerenone and spironolactone), neutral

endopeptidase inhibitors, antidiabetic agents (such as insulin, sulfonylureas (such as glyburide, glipizide and glimepiride), glitazones (such as rosiglitazone and pioglitazone) and metformin), cholesterol lowering agents (such as atorvastatin, pravastatin, lovastatin, simvastatin, clofibrate and rosuvastatin), and alpha-2-delta ligands (such as gabapentin, pregabalin, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1 α ,3 α ,5 α)-(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-amino-5-methyl-octanoic acid).

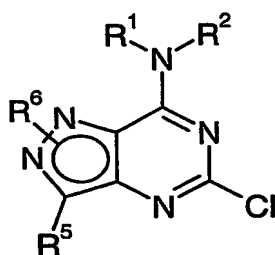
66. Use of a compound of formula (I) as claimed in any one of claims 1 to 54, or a pharmaceutically acceptable salt, solvate or polymorph thereof, in the preparation of a medicament combined with a second pharmaceutically active agent selected from aspirin, angiotensin II receptor antagonists (such as losartan, candesartan, telmisartan, valsartan, irbesartan and eprosartan), calcium channel blockers (such as amlodipine), beta-blockers (i.e. beta-adrenergic receptor antagonists such as sotalol, propranolol, timolol, atenolol, carvedilol and metoprolol), C11027, CCR5 receptor antagonists, imidazolines, sGCa's (soluble guanylate cyclase activators) antihypertensive agents, diuretics (such as hydrochlorothiazide, torsemide, chlorothiazide, chlorthalidone and amiloride), alpha adrenergic antagonists (such as doxazosin), ACE (angiotensin converting enzyme) inhibitors (such as quinapril, enalapril, ramipril and lisinopril), aldosterone receptor antagonists (such as eplerenone and spironolactone), neutral endopeptidase inhibitors, antidiabetic agents (such as insulin, sulfonylureas (such as glyburide, glipizide and glimepiride), glitazones (such as rosiglitazone and pioglitazone) and metformin), cholesterol lowering agents (such as atorvastatin, pravastatin, lovastatin, simvastatin, clofibrate and rosuvastatin), and alpha-2-delta ligands (such as gabapentin, pregabalin, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1 α ,3 α ,5 α)-(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid,

(3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-amino-5-methyl-octanoic acid), for the treatment of a disease or condition where inhibition of PDE5 is known, or can be shown, to produce a beneficial effect.

67. Use according to claim 66 of a compound of formula (I) as claimed in any one of claims 1 to 54, or a pharmaceutically acceptable salt, solvate or polymorph thereof, in the preparation of a medicament combined with a second pharmaceutically active agent selected from aspirin, angiotensin II receptor antagonists (such as losartan, candesartan, telmisartan, valsartan, irbesartan and eprosartan), calcium channel blockers (such as amlodipine), beta-blockers (i.e. beta-adrenergic receptor antagonists such as sotalol, propranolol, timolol, atenolol, carvedilol and metoprolol), CI1027, CCR5 receptor antagonists, imidazolines, sGCa's (soluble guanylate cyclase activators) antihypertensive agents, diuretics (such as hydrochlorothiazide, torsemide, chlorothiazide, chlorthalidone and amiloride), alpha adrenergic antagonists (such as doxazosin), ACE (angiotensin converting enzyme) inhibitors (such as quinapril, enalapril, ramipril and lisinopril), aldosterone receptor antagonists (such as eplerenone and spironolactone), neutral endopeptidase inhibitors, antidiabetic agents (such as insulin, sulfonylureas (such as glyburide, glipizide and glimepiride), glitazones (such as rosiglitazone and pioglitazone) and metformin), cholesterol lowering agents (such as atorvastatin, pravastatin, lovastatin, simvastatin, clofibrate and rosuvastatin), and alpha-2-delta ligands (such as gabapentin, pregabalin, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1 α ,3 α ,5 α)-(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-amino-5-methyl-octanoic acid), for the treatment of a disease or condition selected from hypertension (including essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension), congestive heart failure, angina (including stable, unstable and variant (Prinzmetal) angina), stroke, coronary artery disease, congestive heart failure, conditions of reduced blood vessel patency (such as post-percutaneous

coronary angioplasty), peripheral vascular disease, atherosclerosis, nitrate-induced tolerance, nitrate tolerance, diabetes, impaired glucose tolerance, metabolic syndrome, obesity, sexual dysfunction (including male erectile disorder, impotence, female sexual arousal disorder, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual pain disorder, female sexual orgasmic dysfunction and sexual dysfunction due to spinal cord injury), premature labour, pre-eclampsia, dysmenorrhea, polycystic ovary syndrome, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, chronic obstructive pulmonary disease, acute respiratory failure, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, gut motility disorders (including irritable bowel syndrome), Kawasaki's syndrome, multiple sclerosis, Alzheimer's disease, psoriasis, skin necrosis, scarring, fibrosis, pain (particularly neuropathic pain), cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and haemorrhoids.

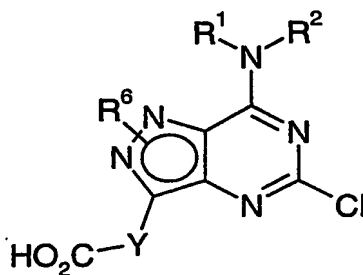
68. A compound of formula (II)



(II)

wherein R^1 , R^2 , R^5 and R^6 are as defined in claim 1.

69. A compound of formula (III)



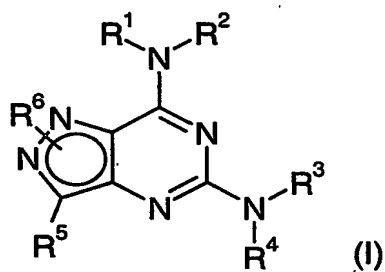
(III)

wherein R^1 , R^2 , R^6 and Y are as defined in claim 1.

Abstract

Novel Pharmaceuticals

This invention relates to compounds of formula (I)



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